

The optimisation of HbA_{1c} testing in UK primary care

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A thesis submitted for the degree of Doctor of Philosophy

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I dedicate this thesis to my three wonderful children, Joseph, Emily and Christopher.

You were so proud of me when I was awarded the fellowship to do this work and you have been with me throughout this journey.

Next it will be my turn to watch you get your wings and fly!

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Abstract

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Background. HbA_{1c} monitoring to guide diabetes management usually requires more than one clinic appointment. Point-of-care (POC) testing allows testing and treatment changes in a single appointment, but trials of POC HbA_{1c} testing have not been shown to benefit patients and the healthcare system. This work explores how HbA_{1c} testing in primary care could be streamlined using POC testing. It comprises four pieces of work and is guided by complex intervention and test-evaluation frameworks.

Methods. Database analyses were used to describe current practice in HbA_{1c} testing and identify factors associated with testing schedules not recommended by guidelines. Systematic review and meta-analysis was used to determine the most accurate POC device. A device was selected to use in a feasibility study to determine how POC HbA_{1c} testing can be used in primary care consultations. Data on recruitment, care pathways, care delivery, satisfaction and behaviour were gathered using data collection forms and questionnaires. Qualitative interviews with patients and clinicians explored perceptions and barriers to POC testing.

Results. Database analyses showed that high or low HbA_{1c} testing rates are associated with previous HbA_{1c} levels and use of incentive schemes. Most POC HbA_{1c} devices have a mean negative bias and large variability compared to laboratory methods. When POC HbA_{1c} testing was used in GP practices, nurses used the result to make clinical decisions during the consultation. Nurse consultations were longer than GP consultations (22mins versus 11mins) and POC results were successfully uploaded to patient records. Patients liked POC testing and found it convenient. It helped some link their HbA_{1c} result to recent behaviour. Clinicians found the tests easy to use but were concerned about cost.

Conclusion. POC testing can be effectively delivered in primary care but funding mechanisms are needed to encourage adoption. This work could inform the design of a randomised trial to test the effect on patient outcomes.

Chapter 1 HbA_{1c} testing in primary care

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1.1 Preface

My interest in this subject area originated from my involvement in several diabetes research projects during my employment as a researcher at the University of Oxford's Nuffield Department of Primary Care Health Sciences. In particular, the lack of an evidence base for recommendations on the frequency of HbA_{1c} testing came to light, as did the recognition that many previous point-of-care HbA_{1c} trials had aspects of their design which may have limited their ability to test the efficacy of point-of-care (POC) testing. My previous employment in a medical diagnostics company working with these technologies meant that I had a pre-existing interest in research in this area. This led to me wanting to understand and improve the way HbA_{1c} is tested. The research presented in this thesis aims to develop an in-depth knowledge of POC HbA_{1c} testing and uses a framework to test how POC HbA_{1c} testing may affect care pathways and patient and clinician behaviours. Results from this work could be used to underpin future effectiveness studies and inform the design of a future UK-based trial of POC HbA_{1c} testing.

Carrying out this research has allowed me to consolidate experience and knowledge accumulated during my time working in academia with previous work in industry, as well as acquire new skills which I will be able to apply in my future career in diabetes research.

1.2 Background and rationale

1.2.1 What is HbA_{1c}?

Diabetes is a growing health problem which currently affects 382 million people globally, equating to 8.3% of adults, and is forecast to rise to 592 million by 2035 (1). Diabetes and its complications pose a major financial burden to healthcare systems (1-3). In the United Kingdom (UK), the National Health Service (NHS) treatment costs for diabetes amount to £13.8 billion annually (2); in the United States, the costs for diabetes care in 2013 were

$548 billion (1). Around 80% of diabetes-related healthcare costs in the UK arise from inpatient care and medication costs for treating complications arising from diabetes, which amount to around £1800 per in-patient. Monitoring and management are relatively cheap, accounting for around 17% of total NHS spend in diabetes (2, 4-7) totalling around £300 per patient per annum. For type 2 diabetes, annual costs of primary care consultations were estimated to be £950 million per year in 2010/2011, which is around 11% of the total spending on type 2 diabetes (8). Medication costs were around £700 million (around 8% of total costs), whereas costs of complications were estimated to be £7 billion per year for this group (8). Maintaining good glycaemic control, through regular monitoring and treatment with glucose-lowering medications, can reduce the risk of developing future complications (5, 9, 10), and thus reduce the occurrence of expensive hospitalisations.

The purpose of monitoring is to lower blood glucose levels, which increase over time in those with diabetes. Individuals at an early stage of type 2 diabetes treatment are often referred to as "diet-controlled". As levels of glycaemia increase and reach a threshold, medication is used. Metformin, an orally-administered glucose-lowering medication, is usually the first to be introduced (11, 12). Other oral or injectable medications may later be added to, or used in place of, metformin. Insulin would usually be the final treatment offered if targets are not being reached.

Glycaemic control is monitored in people with diabetes by measuring glycated haemoglobin or haemoglobin A_{1c} (HbA_{1c}), which is formed when glucose binds with haemoglobin within blood erythrocytes (13, 14). The formation of HbA_{1c} is reported to take place slowly over the 120-day lifespan of an erythrocyte (13), and HbA_{1c} is widely believed to represent glycaemia over the past 2-3 months (15). HbA_{1c} testing may be used either to diagnose diabetes (16), or for long-term monitoring of glycaemic control in people with established diabetes, to guide treatment. It has the advantage over blood

glucose in that it is not prone to daily fluctuations and biological fluctuations (17, 18), and elevated levels of HbA_{1c} have been shown to predict complications in diabetes (10). Monitoring of HbA_{1c} in people with type 2 diabetes usually takes place in primary care settings where the patient needs to attend to have a venous blood sample taken, which is sent for analysis in a central laboratory. The test result is reported back to the clinician within a few days, and the patient is then often required to make a second visit to the health centre or clinic to discuss the result with the physician or specialist nurse. In some cases, if the HbA_{1c} test result is below the patient's target level, the patient may not need to attend the surgery or clinic again, and may therefore remain unaware of their actual HbA_{1c} value.

Measurement of HbA_{1c} usually takes place in central laboratories using one of three methods: cation exchange chromatography, affinity chromatography or immunoassay (described in greater detail in Chapter 3). Until 2009, HbA_{1c} was measured internationally in percent units, which are % of the total haemoglobin concentration in the blood. These units are referred to as NGSP units (mainly US) or DCCT units (mainly Europe). In 2009 this was standardised in Europe by the International Federation of Clinical Chemistry (IFCC) to new units reported as mmol/mol (19-22). This avoids confusion as to whether HbA_{1c} is being reported as an absolute value or as a relative value in %. There is a conversion factor to convert between these units. Now, dual reporting of HbA_{1c} in both units is required across most of Europe (23).

1.3 HbA_{1c} monitoring in primary care

Regular HbA_{1c} monitoring is pivotal to diabetes care. Guidelines currently recommend monitoring of HbA_{1c} every 3-6 months in people with type 2 diabetes until the HbA_{1c} is stable or unchanging, and at 6-monthly intervals once the HbA_{1c} level and blood glucose

lowering therapy are stable (11, 12, 24). However, there is no real patient data available in the peer-reviewed literature to underpin these recommendations, and some studies suggest that HbA_{1c} may change more quickly than previously thought (25, 26). Moreover, it has been shown that changes in HbA_{1c} 12 weeks after a change in medication can be predicted at earlier time intervals (27).

In the UK, the Quality and Outcomes Framework (QOF) is an incentive scheme which rewards GP practices for the percentage of patients who are meeting treatment targets through remuneration. In diabetes, reimbursement is contingent on testing HbA_{1c}, as well as other indicators, in all patients every 12 months. This is intended to encourage GPs to monitor their patients at least annually.

Although guidelines recommend that HbA_{1c} should be measured every three to six months, there are several recent reports suggesting that these are not always adhered to, and that HbA_{1c} tests are being performed at shorter time intervals (26, 28-30). Driskell and colleagues (30) reported that over 11,000 HbA_{1c} tests were performed more frequently than recommended by NICE guidelines in University Hospital of North Staffordshire during 2010. These frequent tests accounted for around 21% of all laboratory requests for HbA_{1c} measurement. Over 80% of these requests came from primary care and interestingly, over two thirds of the more frequent requests were for patients who had well-controlled diabetes. In contrast to this, over 14,000 requests from primary care were made later than guidelines recommend (30), and the majority of these were in patients whose diabetes was poorly controlled.

In light of this, it is apparent that little is known about actual testing behaviour for HbA_{1c}. In order to better understand how a new intervention might affect clinician behaviour, in-depth knowledge of how GPs currently use HbA_{1c} tests in monitoring their patients is

needed. This could be explored through an analysis of a national primary care database to describe HbA_{1c} testing and quantify how many tests are taking place outside guidelines. Of particular interest, would be to explore how testing differs relative to patient- and GP-level factors.

1.4 Point-of-care testing

A patient and participant survey carried out via the Diabetes Research Network in Oxford in 2012, to inform a project at University of Oxford, found that many patients viewed having to travel twice to the GP surgery for an HbA_{1c} test as an inconvenience. This is supported by similar reports in the literature (31, 32). A range of new technologies have emerged in recent years which allow the rapid measurement of HbA_{1c} in the GP surgery. Point-of-care (POC) tests are typically bench-top devices designed for use in an office, treatment room or at the bedside, and use a finger-prick blood sample to provide a rapid test result within a few minutes. These devices usually use affinity chromatography or immunoassay analysis methods (which are described in more detail in Chapter 3).

These technologies contribute to a more streamlined, and thereby potentially improved, patient-clinician encounter, because performing the test, discussing the test result, and making any necessary medication changes, can take place within a single consultation (33). As well as its use in conventionally structured primary care appointments, new and changing models of care are now emerging, in which POC testing could potentially play an important role. The NHS five-year forward view (34) points out the need for greater integration across different aspects of care, which should include increasing out-of-hospital care and improving integration of services around the patient. This may manifest as GPs providing more testing, volunteers providing support for people with long-term conditions, or closer integration between GP and social care services; any of which could

make use of POC testing. Some pharmacists are already beginning to provide some POC testing services to aid appropriate prescribing, for example C-reactive protein testing prior to antibiotic prescribing for sore throats (35).

POC HbA_{1c} devices have been evaluated in some health care settings (25, 36-38), but few studies have been carried out in the UK, where widespread adoption of these technologies has been slow. A recent survey identified diabetes amongst a number of conditions for which GPs felt there was a clinical need for POC testing. Barriers to adoption included concerns about accuracy and perceived lack of capacity to alter consultations (39).

In section 1.5, I present a review of the literature summarising specific considerations of POC testing in general, what is known about POC HbA_{1c} testing in particular, and identify gaps in current knowledge.

1.5 Point-of-care testing – benefits and barriers

1.5.1 Introduction and overview of POC testing

'Near-patient testing' (NPT) and 'Point-of care testing' (POC) are terms used synonymously to define "*analytical procedures performed for patients by healthcare professionals outside of the conventional laboratory*" (40). This can include tests that take place in hospital wards, general practice surgeries, pharmacies, or patients' homes. Use of point-of-care testing in general practice enables rapid decisions to be made in the consulting room without the delay of waiting for results from a laboratory. In hospital settings, it has been demonstrated that rapid turnaround times for test results correlate with length of stay in emergency departments (41).

POC testing has been extensively adopted across different settings covering a number of disease areas: blood glucose testing in diabetes has been widely adopted for home use (42); international normalised ratio (INR) testing for warfarin therapy (43), and C-reactive

protein (CRP) testing prior to prescribing antibiotics, are increasingly used in GP surgeries (44); whereas cardiac troponin testing is used in emergency or intensive care settings (45). Some tests are used most frequently for monitoring and treatment adjustment (INR), whereas others are used for screening or diagnosis, for example CRP for bacterial infection, or cardiac troponin for myocardial infarction.

In primary care, POC testing has the potential to improve the quality of care delivered to patients by making care more patient-centred and allowing testing and clinical decisions to be made in a single appointment. Rapid test results expedite clinical decision making, facilitate the feedback of results to patients, and allow shared decision making. This is more convenient to patients, and may be particularly important for people with chronic conditions such as diabetes, who require regular monitoring (46). In by-passing the time-consuming process of sending a sample to a central laboratory, POC testing may have other advantages over conventional testing, by providing opportunities to discuss the result and improve education. Patient-centred approaches to diabetes care have been linked to clinically significant reductions in HbA_{1c} (47), and interventions involving patient collaboration and interaction are more effective in motivating patient self-care (48). Patients receiving POC testing are reported to have a stronger relationship with their GP, are more motivated to look after their condition (32), and have better medication adherence than those in usual care (49).

If the accuracy of a POC test is inferior to a standard laboratory method, then this could influence the treatment decisions made, or change the numbers of cases of the target condition detected; either of which could go on to affect patient outcomes. The impact of accuracy on the number of people diagnosed using a POC test could be estimated using a diagnostic accuracy study, in which all study participants receive both the POC test and the laboratory test. This study design would allow differences between the numbers of

people above and below a diagnostic threshold to be compared for each of the tests, but would not provide any information on how the result may be used by the clinician in terms of treatment or referrals. A study to examine how POC testing may impact on treatment decisions and patient outcomes, would need to be a parallel-group study. This design would allow comparisons in outcomes between groups of patients who receive POC testing and those who receive usual care. This could be best achieved in a randomised controlled trial in which selection bias is minimised by randomly allocating patients to each of the groups (50). However, before evaluating in a randomised trial, it is first important to understand ways in which the test may affect patient health, to ensure that the test is used optimally and implemented in the right way (51).

Although some POC technologies have been widely adopted, there remains an unmet clinical need for a greater range of POC tests to assist clinicians with immediate decisions (52). The reasons behind the slow rate of adoption will differ between disease areas. Moreover, differences in funding or reimbursement mechanisms in different countries will also affect the rate of uptake. The remainder of this chapter focusses on issues around POC testing and how it may affect the patient consultation and patient outcomes.

1.5.2 Training, quality control and patient safety

Training, patient safety, quality control and maintenance all need to be carefully considered when adopting POC technologies. Because there are fewer steps in the testing process, POC testing may be perceived to reduce opportunity for generating errors; however, the majority of errors in the patient testing pathway take place outside the laboratory (53). Adequate training of operators is therefore essential to minimise human error caused by incorrect sample-taking, mixing up patient data or incorrect storage of cartridges or strips (54). Mis-reporting of results could be a source or error in POC testing, but because many devices have connectivity potential, enabling a direct connection

between the POC device and electronic patient records, this can be minimised as a source of error (53). Training, quality control and quality assurance of instrumentation are usually only undertaken by central hospital laboratories, and so are not generally a consideration in primary care. If POC technologies are used in GP settings, these could be managed in-house, but central management by a specialised point-of-care team may be preferable (54). Although many hospital laboratories have point of care teams in place to manage instruments located within the hospital, this may not have been addressed to the same extent for instruments located in primary care settings (55). Some countries have adopted frameworks or guidance for the use of POC testing (56), to provide guidelines on performance of instruments, training or quality control (40).

1.6 What is known about point-of-care HbA_{1c} testing

Point-of-care tests for HbA_{1c} have been available for several years. Research findings have been published on the impact of POC HbA_{1c} testing on clinical decision making and clinical outcomes, costs, satisfaction and qualitative research studies, health economic evaluations and accuracy studies. Each of these is discussed below.

1.6.1 Impact of POC HbA_{1c} testing on clinical decision making

Only two published trials reported the effect of POC HbA_{1c} testing on clinical decision making (57, 58). In 1999, a Health Technology Assessment report from the UK compared differences in management decisions between near-patient HbA_{1c} testing and usual care in patients attending a routine diabetes clinic in a hospital setting (57). They found that for those with good glycaemic control (HbA_{1c}<7.5%, 58 mmol/mol), there were no differences in the proportion of patients who received a change in management between the near-patient testing and control arms of the study. They did, however, find that for those with a baseline HbA_{1c}>7.5% (58 mmol/mol), a significantly higher proportion of

patients in the near-patient testing arm received a management change compared with those in the control arm (odds ratio: 1.75, 95% Confidence interval, CI 1.12-2.72). In 2003, a non-randomised trial in the US found that patients with $HbA_{1c} \geq 7\%$ (53 mmol/mol) were more likely to have their diabetes therapy intensified with POC testing compared with those in routine management (58).

These reports, along with findings from other non-randomised studies, were summarised in a review from 2005 (59). It concluded that the use of POC HbA_{1c} testing was more likely to result in intensification of therapy, both for those patients with substantially elevated HbA_{1c} (>8% or 64 mmol/mol), and for those with mildly elevated HbA_{1c} at baseline. It also concluded that therapy was less likely to be intensified inappropriately if POC testing was used.

1.6.2 HbA1c and clinical outcomes

Few trials have reported the effect of POC testing on HbA_{1c} and, despite the apparent effect of POC testing on treatment intensification, a systematic review published in 2011 (4) did not find a statistically or clinically significant benefit of POC testing on HbA_{1c} in three trials (60-62) of over 2000 patients. The authors suggested that limitations in the design of the included trials may have contributed to the failure to identify an effect. One of the limitations was that some trials recruited patients who had well-controlled diabetes at baseline. Furthermore, of the included trials, two recruited only patients who were insulin-treated (60, 62) and the other trial recruited a combination of type 1 and type 2 diabetes patients (61), meaning some patients were insulin users. There were no studies which separately examined data only from patients who were not insulin-treated. People who are insulin-treated usually self-monitor their blood glucose levels and adjust their insulin dose accordingly in addition to HbA_{1c} monitoring.

Two studies reported numbers of hypoglycaemic episodes and emergency admissions, and found no difference between those using POC testing compared with usual care (60, 62). There have not been any studies to date which have assessed the impact of POC HbA_{1c} testing on long-term outcomes.

1.6.3 Summary of patient satisfaction

A trial in the UK used questionnaires to measure difference in patient satisfaction for those allocated to near-patient testing compared with conventional testing (57). Patients in the near-patient testing group were significantly more satisfied with the information provided by staff and how they were treated as a person by staff, compared with the conventional testing group. All other factors were similar between the groups.

Patient satisfaction was measured using questionnaires as part of an Australian randomised trial comparing POC HbA_{1c} testing with usual care (32). Those using POC testing were, in general, more satisfied than patients in control groups; they preferred having a finger-prick blood sample, not having to travel, and having immediate feedback. They were also more motivated to manage their condition, and had an improved relationship with their GP.

1.6.4 Qualitative studies

Semi-structured interviews were conducted with ten doctors, who were involved in a UK-based trial, to get views on possible advantages or disadvantages of the near-patient testing service (57). The majority of the doctors thought that having an immediate HbA_{1c} result was an advantage, which improved organisational efficiency, helped them to make more confident clinical decisions, and they reported that they were more likely to take action on results that were out of range.

As part of another UK-based randomised trial of POC testing versus usual care, semi-structured qualitative interviews and questionnaires were used to gauge acceptability and satisfaction with point-of-care testing (63). It was found that patients in both study groups had a limited understanding of the HbA_{1c} test, and were typically satisfied with their usual test arrangements. Nurses thought that having the result available for discussion was an advantage for patient education, improved their job satisfaction, and helped to avoid missed results and loss to follow-up.

In 2004, interviews were conducted with a cohort of healthcare professionals and people with diabetes in Canada, to explore ideas, opinions and expectations of POC testing in diabetes management (31). Although the interviewees were not end users of POC testing, in general perceptions were very positive, and improved communication by receiving information face-to-face and immediacy of results were viewed to be very important. Amongst the potential barriers highlighted by patients, were the importance of accurate results. Accuracy was also raised as the primary concern by most health care professionals, although costs may be the deciding factor on whether POC testing would be implemented. Both costs of instrument purchase and those of re-organising clinics were regarded as areas for concern. Locating the instrument where it would be accessible to everyone was also raised as a potential problem.

1.6.5 Cost-effectiveness of POC HbA_{1c} testing

The costs of POC testing are generally perceived by healthcare providers to be higher than usual care (43, 64). Evidence of a clinical benefit may therefore be necessary for these technologies to be deemed cost-effective. POC testing in many scenarios, may have its greatest impact on cost savings by reducing costly hospitalisations, or reducing hospital length of stay. St John and Price conclude their overview of economic evidence of POC testing, by suggesting that the limited evidence on costs of POC testing are in part due to a

lack of understanding of the clinical effectiveness (64). They highlight the need to understand care pathways and how these may be affected by POC testing.

Reports suggest that POC testing is perceived to be expensive in terms of the cost-per-test (65). A UK study compared the costs of conventional HbA_{1c} testing and near-patient nurse-based testing (57). The cost per visit was calculated to be £14 for conventional testing and £17.91 for near-patient testing. Patients who used the POC testing had fewer tests per year than usual care patients, though it could not be certain whether this was a direct consequence of the POC testing. Data on patient costs related to the time spent in the clinic, including waiting time, were collected by questionnaire. It was found that patients spend about three minutes longer, on average, in point-of-care consultations than in usual care. This study was, however, conducted in a hospital-based diabetes clinic; these findings may therefore not be representative of costs in primary care settings.

A 12-month UK primary care trial of 630 patients compared costs of diabetes medication, consumables, contact with GP surgery staff, numbers of HbA_{1c} tests, and contacts with the hospital, between POC groups and usual care (66). Overall, diabetes-related care costs were found to be slightly lower for the POC testing group compared with the usual care group, but the difference was not statistically significant (£370.46 per patient compared with £389.58 per patient respectively). The cost of the HbA_{1c} test itself was higher, but this was balanced by savings in contacts with the hospital.

In 2010, a group in Australia (67) carried out a cost effectiveness analysis of POC HbA_{1c} testing as part of a trial of 4968 patients in general practice. The health outcome they evaluated was the proportion of patients within therapeutic range at the end of the trial. The analysis found that POC testing was more effective. Points in the analysis were distributed between the two right-hand quadrants in the cost-effectiveness plane diagram,

which infer higher costs but high effectiveness and low cost and high effectiveness. The point estimate showed higher costs per patient than usual care, but this was not significant. Total costs per patient after 18 months were AUS$3676 for POC testing versus AUS$3672 for usual care. When cost components were separately examined, POC testing costs (including purchase of cartridges) were AUS$137 higher per patient than usual care. Whereas the major cost savings were in reducing hospital admissions, which were AUS$334 lower per patient in the POC testing arm than in usual care, but this cost difference was not significant.

More recently, a report from Ontario in Canada estimated costs of replacing laboratory HbA_{1c} testing with POC HbA_{1c} testing for monitoring glycaemic control (68). It reported that this would save an estimated $4.7 million over the period of 2013-2014, but the methods used in this analysis were not well-reported. The patient-borne costs were similar in both groups.

These studies suggest that costs associated with POC HbA_{1c} testing do not differ substantially from usual care. Costs of delivering the test may be higher, but these may be offset by savings resulting from fewer hospital encounters. How these costs are affected by longer-term outcomes, or how they may differ in different subgroups of patients, has not yet been studied.

1.6.6 Accuracy of POC HbA_{1c} tests

According to Larsson *et al.* (54), to benefit from POC testing, a prerequisite is that the "*test is sufficient for medical decision-making in the clinical setting and should not necessitate additional confirmatory tests*." There has been a wealth of literature reporting the accuracy of different POC HbA_{1c} test devices, the majority of which have been laboratory-based evaluations (69, 70). Fewer studies have assessed device performance at

their intended point of care setting or with clinicians or carers carrying out the tests (25, 36-38). The suitability of many of these devices for the accurate measurement of HbA_{1c} has been questioned, with some commercially available POC HbA_{1c} tests reported not to meet accepted criteria for accuracy and precision (69, 71). The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have suggested that ideal precision goals for HbA_{1c} should be a coefficient of variation (CV) of <2% (72); however a CV of up to 3% is still considered reasonable (14, 73).

The only published report which has attempted to combine accuracy data from multiple studies identified a mere five studies for inclusion, covering three devices, and combined correlation coefficients between the included studies (74). Although this type of analysis goes some way to helping the reader assess the degree of scatter in data contributing to the correlation coefficient, it provides no information on its agreement with the laboratory measure. To achieve this, a different approach is needed. Systematically reporting and pooling data estimates of bias and precision between POC HbA_{1c} devices and laboratory measurements would enable laboratories and clinicians to compare analysers and make a judgement on which best meet their analytical performance needs (75, 76). This may be of particular importance for clinicians in primary care settings where much of the management of people with type 2 diabetes takes place. The comparison of accuracy between devices over the entire therapeutic range could be carried out by combining data on measurement error (bias) or mean biases between index and reference tests (76-78). A well-conducted comparison of POC device accuracy would both provide a picture of how these devices perform in general compared to laboratory methods, and help end users to make an informed choice on which device to select for use in clinical practice.

1.6.7 Summary and what next?

In summary, POC HbA_{1c} testing shows potential for use in general practice. Patients and clinicians view it favourably, costs seem to be comparable to usual practice, and there is evidence supporting improved motivation and adherence to taking medications, which could lead to improved outcomes. Evidence for adequate accuracy of devices, costs of adoption and on-going costs of POC testing in primary care, as well as evidence of a clinical benefit, are less convincing. Furthermore, these technologies have not been widely adopted in the UK, with around 17% of UK practices reported to use POC HbA_{1c} testing (52). There are several factors which may have contributed to this slow rate of uptake: reluctance to change current practice, concerns about accuracy, or no incentives to adapt funding mechanisms because, as yet, there is no evidence of a clinical benefit.

In a recent survey, GPs identified POC testing for diabetes as one of the most potentially useful tests for monitoring, diagnosis and reducing hospital admissions (39), suggesting that there is a place for this type of testing in primary care. The required changes in practice may be considered burdensome by some clinicians. If either the technology itself, or the way it is implemented, is not acceptable, or clinician workloads are too high, then widespread uptake is unlikely to take place (79).

As highlighted in section 1.6.2, there is currently insufficient evidence that using POC testing improves HbA_{1c} (4). This does not, however, necessarily imply that POC HbA_{1c} testing is inherently ineffective, but instead may be an artefact of the trial design limiting the possibility of patients benefitting from the intervention. Examples of such limitations are, inclusion of patients with $HbA_{1c} \leq 7\%$ at baseline, or not feeding back and acting on the POC test results during the patient consultation. Feeding back results to the patient and using the POC result to make clinical and treatment decisions during the POC consultation is reported to be essential to the efficacy of POC testing (80). Patients who are aware of

their own HbA1c and goals have better glycaemic control and self-management behaviours (81-83). Hence, opportunities to maximise the benefits of POC testing may have been missed in some previous trials.

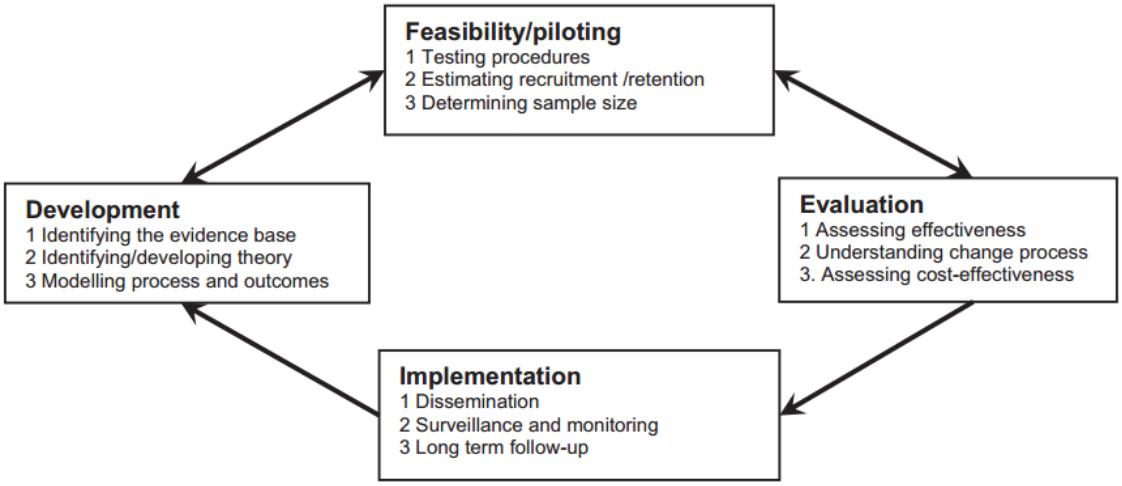
Any future trial of POC HbA_{1c} testing would need to be carefully designed to ensure that all the interacting components are considered. The impact of the new test-treatment pathway on clinical decision-making, and other intermediate outcomes by which it can affect health, need to be considered. A framework for designing and evaluating tests has identified several key mechanisms through which testing can change patient health outcomes (51). These include altering clinical decisions and actions, changing timeframes to decisions and actions, and the influence of these on clinician and patient perceptions. The framework separately examines how individual components may affect patient outcomes, and can be used to inform the design of trials. In addition to examining the test-treatment pathway, it is also essential to measure the efficacy of POC testing in everyday practice and, because behaviour change in those delivering and receiving the intervention is required, understanding the range of effects, and how these may vary between people or sites is important. To achieve this, the Medical Research Council (MRC) has developed a framework for evaluating complex interventions (84-86), the process of which is explained in more detail in the following section.

1.7 Evaluation of complex interventions

The MRC describes interventions containing several interacting components, which may include aspects of behaviour, as complex interventions (84, 85). The guidance for evaluating complex interventions recommends acquiring a good theoretical understanding to identify weak links in the causal chain. Steps include carrying out a process evaluation to identify possible implementation problems, collecting data on variability for individual

level outcomes, measuring a range of outcomes to pick up unintended consequences, and allowing a degree of adaptation between settings. These steps take place in phases, which are not necessarily linear (Figure 1.1).

Figure 1.1 - Key elements of the development and evaluation process from MRC guidance for developing and evaluating complex interventions (85).



The successful introduction of POC HbA_{1c} testing into a GP consultation is contingent on patient and clinician behaviour change to administer the test and act on the result, and thus it can be described as a complex intervention. As it is not yet clear how POC testing would work in everyday practice, it is important to understand the full range of effects, and how these may vary with time, setting and recipients. This would require a series of preparatory steps to understand more about the different components of the intervention and how they may work (84). These steps include developing a theoretical understanding (the Development phase in Figure 1.1), and evaluating components of the intervention such as acceptability, compliance, delivery of the intervention, as well as recruitment, retention and its potential impact on behaviour change (the Feasibility/piloting phase in Figure 1.1).

1.8 Thesis outline

During my DPhil I have worked in line with early stages of the MRC guidance for complex interventions (84, 86, 87) to assess the feasibility of using POC HbA_{1c} testing in UK primary care consultations. In addition, I have followed the framework for assessing the value of diagnostic tests (51). Using these frameworks, the work presented in this thesis examines how POC HbA_{1c} testing may directly and indirectly impact on care pathways, treatment decisions, patient perceptions and patient and clinician behaviours. This structured approach will improve the understanding of the mechanisms by which POC testing may change patient outcomes, and thus increase the knowledge about how these tests could best be used in the future.

In order to complete this project, I have worked closely with several colleagues at The Nuffield Department of Primary Care Health Sciences in Oxford who have expertise in working with large databases, systematic reviews, managing clinical data collection studies and qualitative research. I attended several courses which have given me the skills to carry out this work, these covered: diagnostic accuracy systematic reviews and meta-analysis, multilevel statistical models, linear and logistic regression, survival analysis, basic epidemiology, and qualitative research methods.

1.9 Research aim and objectives

Aim: To understand how HbA_{1c} testing in UK primary care could be streamlined and optimised using POC HbA_{1c} testing.

To achieve this, I have followed the framework for evaluating new tests and the MRC guidance for complex interventions, by carrying out the following:

1. An in-depth study to understand current practice in HbA_{1c} testing using both a local and a national database to describe HbA_{1c} testing patterns, quantify the

amount of testing which takes place outside guidelines, and identify factors which are associated with HbA_{1c} testing outside guidelines (Development phase).

2. A summary of POC HbA_{1c} test devices and a systematic review and meta-analysis of accuracy and precision of POC devices, with the objective of using the results to select a device to use in a data collection study (Development phase).

3. A feasibility study to determine whether POC HbA_{1c} testing can be introduced into diabetes consultations in UK primary care, and gather data on recruitment, care pathways, care delivery, patient satisfaction and behaviour, using data collection forms and questionnaires (Feasibility phase).

4. Qualitative interviews with a selection of patients and clinicians involved in the feasibility study to understand perceptions and potential barriers to POC testing (Feasibility phase).

This work will improve knowledge on POC HbA_{1c} testing which will help to inform future study designs.

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Chapter 2 : Description of current practice in HbA_{1c} testing

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2.1 Introduction

This chapter will examine current practice in HbA_{1c} testing in the UK and report patterns in HbA_{1c} testing frequency. I am particularly interested in reporting how frequently HbA_{1c} testing takes place in accordance with guidelines and exploring factors which are associated with tests being carried out too frequently or not frequently enough. To achieve this, I will use two datasets, one from the John Radcliffe Hospital in Oxford, and the second from the Clinical Practice Research Datalink (CPRD), a national database of records from 680 GP practices across England, Wales and Scotland. I will begin by using laboratory data provided by the John Radcliffe Hospital to find associations between patient and GP-level factors and HbA_{1c} testing outside guidelines to generate hypotheses and to develop the statistical models to be used in the main analysis. These hypotheses will then be tested using the models developed from the hospital dataset in a CPRD dataset of 100,000 patients with diabetes.

2.1.1 Background and rationale

Internationally, guidelines recommend testing HbA_{1c} at three to six monthly intervals in people with type 2 diabetes (1, 2), though prior to issuing new guidelines in 2015, NICE recommended testing every two to six months (3). As discussed in Chapter 1, the evidence behind this testing interval is sometimes attributed to the 120-day life-span of a red blood cell (4) and expert consensus (1). Although there is no consensus on what the optimal frequency for HbA_{1c} testing is (5), it generally thought that there is no value in repeating an HbA_{1c} test within two months. The Quality and Outcomes Framework (QOF) is an incentive scheme which reimburses UK general practices on achievement based on patient health indicators, collecting data annually on 31st March. For diabetes, these currently include monitoring of patients' HbA_{1c} every 12 months (6), whilst prior to 2013/14 this was every 15 months (7). The surgery receives re-imbursement for the percentage of their

diabetes patients who achieve pre-defined HbA_{1c} thresholds in the preceding 12 months. This should encourage practices to monitor their patients at least annually and may have an impact on testing intervals.

Several recent reports suggest that across different countries, guidelines for HbA_{1c} testing are not always adhered to (8-10). An analysis of newly diagnosed patients with type 2 diabetes followed up for 10 years from a British primary care database (11) suggests that many people may have longer intervals between tests than guidelines recommend. Another analysis of HbA_{1c} test requests over a 10-year period from 2001 to 2011 in a North Staffordshire hospital in the UK (9) found that over 50% of all test requests were made either sooner or later than recommended by guidelines. The majority of these requests came from primary care. Similar results had been observed in an earlier study conducted in 2002 to 2004 on data from a diabetes out-patient clinic in Turkey (8). An analysis of HbA_{1c} requests carried out using laboratory data from a hospital in Singapore (10) reported that 42% of HbA_{1c} test requests made to the hospital laboratory in 2006 and 2007 took place less than 90 days from the previous request. A US study found that more than 60% of people with well-controlled diabetes received more tests than necessary (12). These reports suggest that guidelines do not always have an impact on HbA_{1c} testing intervals even though healthcare budgets are facing pressure to reduce costs. In comparison, a recent report from the College of American Pathologists found that in the US the majority of patients had fewer than 8 HbA_{1c} tests in 24 months, which is in accordance with recommendations by guidelines (13). Arguably, monitoring HbA_{1c} more frequently may be appropriate for some patients, particularly in those who have had a recent medication change (14) or those with uncontrolled diabetes.

The work presented here examines patterns in HbA_{1c} testing from primary care in the UK by first analysing data on HbA_{1c} test requests made to an Oxfordshire hospital, then

extending the analysis to a national dataset. The analysis will focus, in particular, on identifying factors which are associated with repeat HbA_{1c} testing taking place outside recommended intervals.

2.1.2 Aims and objectives

The overall aim of this part of the research is to establish which factors are associated with the frequency and timing of HbA_{1c} test requests from general practices in (i) the area served by the John Radcliffe Hospital laboratory, and (ii) a national database, over 10-years. The objectives are

1. To describe HbA_{1c} testing patterns and explore how these vary in subgroups of patients;
2. To explain how HbA_{1c} testing behaviour varies with patient age, sex, previous HbA_{1c}, time of year (relative to QOF reporting) and the requesting general practice;
3. To examine whether patterns in HbA_{1c} testing found in the Oxfordshire cohort are also observed in 100,000 adult diabetes patients from across the UK using the CPRD database;
4. To extend the CPRD analysis to additional patient and GP-level factors on HbA_{1c} testing behaviour.

2.2 HbA_{1c} test requests in Oxfordshire

2.2.1 Methods

Dataset

Approval was obtained from the Caldicott Guardian from the John Radcliffe (JR) Hospital in Oxford for use of anonymised data on HbA_{1c} requests in the 10 years from 1st January 2004 to 31st December 2013. The Head of Clinical Biochemistry and the Laboratory Manager provided anonymised data on: patient number, HbA_{1c} result, date of test, patient age, patient sex and details of requesting GP practice for the purpose of this analysis. The analysis plan was pre-specified and agreed by a group of researchers and laboratory managers in advance of the analysis.

Inclusion/exclusion criteria:

Patients who had a minimum of two HbA_{1c} test requests from primary care from 1st Jan 2004 to 31st Dec 2013 were included in the analysis.

All test requests from secondary care and paediatric clinics were excluded.

Data management

Multiple measurements made on one day for a single identification code were assumed to be quality control (QC) measures and were excluded from the analysis. Because of the introduction of HbA_{1c} in the diagnosis of diabetes in 2011, patients whose first HbA_{1c} test was after 1 January 2011 with HbA_{1c} less than 6.5% (48 mmol/mol), and who had no follow-up tests for more than 2 years, were assumed to be having a diabetes screening test and were excluded from the analysis. Samples with implausible HbA_{1c} results were excluded from the analysis. In consultation with the Head of Pathology at the JR Hospital laboratory, a plausible range for HbA_{1c} was deemed to be 3-16%, corresponding to 9-151

mmol/mol. Age of patients was fixed to age at first visit. For each patient, the GP surgery was fixed as the GP surgery attended at the first visit in the dataset. GP surgeries within the Oxford ring road (Appendix 1.1) were categorised as "Oxford" surgeries; all other surgeries were categorised as "outside Oxford". HbA_{1c} test date was coded relative to QOF dates: tests which took place in the 4 months prior to the QOF deadline of 31st March (December-March) were compared with the rest of the year, as had been pre-specified in the analysis plan.

Outcomes

NICE guidelines stated, until 2015, that HbA_{1c} should be tested at 2-6 monthly intervals, suggesting that re-testing within 60 days of the previous test would be outside recommendations. A 60-day interval was therefore chosen as the lower limit to comply with guidelines. QOF reimbursement is conditional upon re-testing HbA_{1c} within 12 months of the previous test. To account for leap-years, an upper limit of 366 days was used for testing to comply with guidelines. Repeat HbA_{1c} tests which took place within 60 days of their previous test, or were more than one year after the previous HbA_{1c} test, were separately reported.

Descriptive analyses

Data were tabulated to present mean HbA_{1c} (± standard deviation, SD) in % HbA_{1c} units, mean (± SD) testing interval in days and the absolute numbers of tests less than 60 days or more than 366 days from the previous test. Data were presented for all patients, and for subgroups stratified by age, sex and previous HbA_{1c}. The number of tests performed each year and the mean numbers of test requests for each month were plotted in bar charts. Numbers of repeat HbA_{1c} tests taking place <60 days or >366 days from the previous test were tabulated within subgroups of patients categorised by previous HbA_{1c}. Patients with

previous HbA_{1c}<6.5% were defined as having tightly controlled diabetes, patients with HbA_{1c}≥6.5% and <7.5% were classed as having well-controlled diabetes, and patients with HbA_{1c}≥7.5% as uncontrolled diabetes. The numbers of test requests <60 days or >366 days from the previous test in the 2-year periods of 2006-2007, 2008-2009, 2010-2011 and 2012-2013 were also reported so that trends over time could be explored. In each of these 2-year periods the total number of patients with more than 8 tests was reported.

Statistical analyses

Stata 14.1 SE was used to carry out all statistical analyses. Results were reported as mean and standard deviation in the descriptive analysis. Levels of significance between groups were tested using two-sample t-test, tests of proportions or linear regression. A p-value <0.05 was considered to be significant.

Because the data consisted of multiple HbA_{1c} measurements made at different time intervals for each patient nested within many GP practices, 3-level mixed effects models were used. Stepwise univariate and multivariate logistic regression using two separate multilevel models were used to examine whether re-testing <60 days or >366 days from the previous test varied at the patient and GP practice level. Increasing year of age, female sex (compared to male), testing in the 4 months prior to QOF deadline (December to March) compared with the rest of the year, previous HbA_{1c}>7.5% compared with previous HbA_{1c}≤7.5%, increasing year of test and increase in HbA_{1c} between previous two measurements (for those who had a minimum of three HbA_{1c} measures during follow-up) were included in each of the models. Odds ratios and 95% confidence intervals were reported for each variable from the univariate and multivariate models. The fit of each covariate into the model was tested based on significance and tested using the likelihood ratio test, the Akaike information criterion (AIC) and the Baysian information criterion

(BIC) to avoid overfitting. The model with the best fit gives the smallest AIC or BIC number. Logistic regression models were fit using the Stata default of 7 integration points. Results for each variable in the univariate analysis were tested using 20 and 30 integration points to ensure that similar results were obtained. Because of the potential bias of the longitudinal model to favour shorter testing intervals, a sensitivity analysis was carried out using a two-level logistic regression model based on a single random measurement selected from each patient, to ensure that results were robust. This was carried out by using the *runiform* command in Stata to randomly order the HbA_{1c} results and hence select one test result for each patient. A two-level logistic regression model based on the time interval for the randomly selected HbA_{1c} measurement for each patient was then fitted.

2.2.2 Results

A total of 6357 observations were removed because they met the criteria for probable screening tests for diabetes. The final analysis included 49,956 patients with a total of 408,868 HbA_{1c} test requests from 106 GP surgeries. Table 2.1 summarises the results for all tests included in the analysis. The mean age of patients at their first visit was 61.9 ± 15.3 years, 45.9% were women, there were a mean of 8.2±6.7 requests per patient, the mean test interval was 219 ± 188 days and the mean HbA_{1c} was 7.38 ± 1.59% (57.2±17.4 mmol/mol). There were 74,406 tests (20.1% of all repeat tests) which took place at intervals <60 days or >366 days from the previous test (26,107 <60 days and 48,299 >366 days). The number of HbA_{1c} tests increased each year over the 10 years from 2004 to 2013 (Figure 2.1a); there were more than twice as many tests in 2013 compared with 2004. There was some variation in the number of tests performed each month over the year (Figure 2.1b): there were slightly fewer tests performed, on average, in the months of April, August and December coinciding with holiday periods, and slightly more tests in March and October.

Table 2.1 – Summary of results of HbA_{1c} test requests.

	All requests
Total number of patients	49,956
Total number of tests	408,868
Total number of repeat tests	358,912
Number of GP surgeries	106
Age	61.9 ± 15.3
Number of women	22,931 (45.9%)
Mean number of requests per patient	8.2 ± 6.7
HbA_{1c} (%)	7.38 ± 1.59
HbA_{1c} (mmol/mol)	57.2± 17.4
Mean test interval (days)	219 ± 188
Number of tests <60 days	26,107 (7.3%)
Number of tests >366 days	48,299 (13.5%)

Data are n (%) or (mean ± SD)

Figure 2.1 – Bar chart showing (a) the total number of tests each year and (b) the mean number of tests for each month of the year over 10 years of the data.

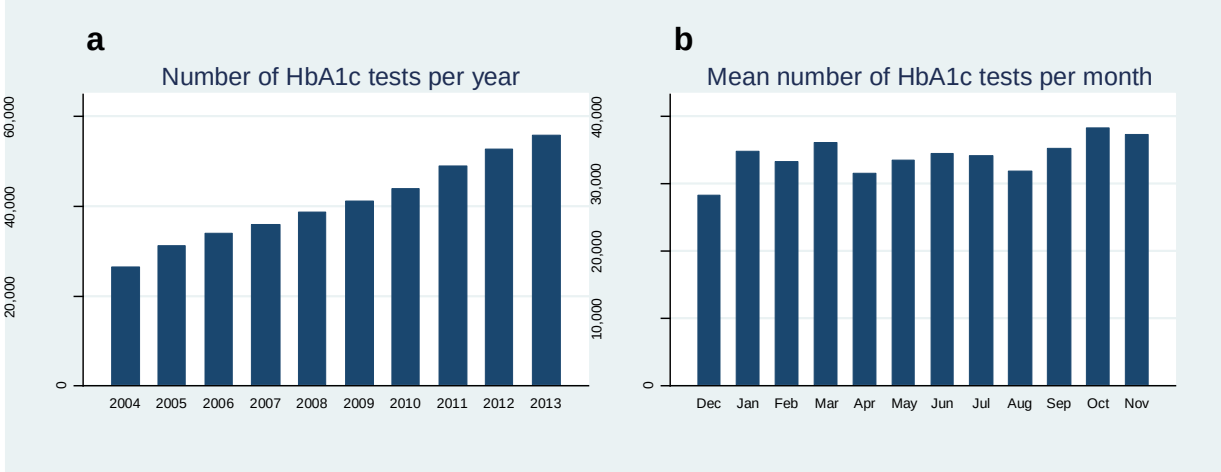


Table 2.2 shows the mean HbA_{1c}, mean test interval and numbers of tests <60 days or >366 days in subgroups of diabetes control, sex, age, and time of year for all test results. Men had slightly higher HbA_{1c} than women (7.41±1.58% or 57.5±17.3 mmol/mol in men compared with 7.34±1.61% or 56.7±17.6 mmol/mol in women) and people aged under 40 had significantly higher HbA_{1c} than those over 40 years of age (7.97±2.05% or 63.6±22.4 mmol/mol and 7.35±1.56% or 56.8±17.1 mmol/mol respectively). For people aged under 40, the mean time interval between tests was longer (247 ± 239 days), and more tests were carried out at time intervals <60 days or >366 days compared with those over 40 (218 ±

186 days). People who had their HbA_{1c} tested between April and November had slightly lower mean HbA_{1c} (7.22 ± 1.58%) than those tested between December and March (7.38 ± 1.65%).

Table 2.2 - Description of repeat test requests stratified by patient characteristics and HbA_{1c} in the Oxfordshire data.

	All repeat requests, N	Mean HbA_{1c} ±SD per patient	Mean test interval ± SD (days)	N (%) of repeat tests <60 days	N (%) of repeat tests >366 days
Tightly controlled: (previous HbA_{1c} <6.5%)	100,906	6.06 ± 0.66	267 ± 216	5331 (5%)	22,005 (22%)
Well controlled: (previous HbA_{1c} 6.5-7.5%)	113,380	7.06 ± 0.81	220 ± 179	6165 (5%)	13,421 (12%)
Poorly controlled: (previous HbA_{1c} >7.5%)	144,626	8.60 ± 1.53	184 ± 166	14,611 (10%)	12,873 (9%)
Male	198,862	7.42 ± 1.53	217 ± 184	14,260 (7%)	26,074 (13%)
Female	159,999	7.37 ± 1.57	221 ± 193	11,839 (7%)	22,219 (14%)
Age < 40 years	15,533	8.02 ± 1.96	247 ± 239	1453 (9%)	2902 (19%)
Age ≥ 40 years	343,379	7.37 ± 1.52	218 ± 186	24,654 (7%)	45,397 (13%)
1 April−30 November	245,286	7.36 ± 1.53	219 ± 188	17,200 (7%)	33,056 (13%)
1 December−31 March	113,626	7.50 ± 1.59	219 ± 189	8,907 (8%)	15,243 (13%)
Number of patients with: 2 tests 3 tests 4-10 tests 11-20 tests 21-50 tests >50 tests	 12,184 5653 16,649 12,447 3023 0				

The HbA_{1c} test interval, stratified by previous HbA_{1c}, is presented in Table 2.3. There were over 11,000 repeat tests carried out within 60 days of the previous test in people with HbA_{1c}<7.5% (representing around 5% of all the tests carried out in people with HbA_{1c}<7.5%). Nearly 13,000 tests were carried out more than a year from the previous

test in people with $HbA_{1c} \geq 7.5\%$ (nearly 9% of all tests in those with $HbA_{1c} \geq 7.5\%$). The most common testing interval was between 180 and 365 days, irrespective of the patient's previous HbA_{1c}; this test interval accounted for 38% of all repeat tests.

Table 2.3 – Numbers of tests carried out at different test intervals stratified by subgroup of previous HbA_{1c}.

	Test Interval							
Previous HbA_{1c}	**<60**	**60-89**	**90-119**	**120-179**	**180-366**	**>366**	**Total**	**Median (IQR) test interval (days)**
All tests	26,107	31,067	44,377	73,671	135,391	48,299	358,912	182 (111,262)
<6.5	5331	4933	7488	17,657	43,492	22,005	100,906	208 (154, 351)
6.5-7.5	6165	7668	11,956	24,717	49,453	13,421	113,380	187 (127,255)
7.5-10	10,475	14,373	20,367	25,823	35,391	9962	116,391	149 (95, 217)
≥10	4136	4093	4566	5474	7055	2911	28,235	132 (81, 223)

IQR – Interquartile range

Table 2.4 – HbA_{1c} testing patterns in two-yearly intervals (from 2006 to 2013).

	2006-2007	**2008-2009**	**2010-2011**	**2012-2013**
Total number of HbA_{1c} tests	69,975	79,805	92,947	108,542
Total number of repeat HbA_{1c} tests	63,397	73,108	84,250	99,900
Number (%) of which:				
<60 days from previous test	4487 (7.1%)	4997 (6.8%)	5696 (6.8%)	7187 (7.2%)
>366 days from previous test	7817 (12.3%)	9534 (13.0%)	11,948 (14.2%)	16,663 (16.7%)
>366 days from previous test & previous $HbA_{1c} < 6.5\%$	2115 (3.3%)	3842 (5.3%)	5875 (7.0%)	9497 (9.5%)
>366 days from previous test & previous $HbA_{1c} \geq 6.5\%$	5702 (9.0%)	5692 (7.8%)	6073 (7.2%)	7166 (7.2%)
>366 days from previous test & previous $HbA_{1c} \geq 7.5\%$	2953 (4.7%)	2785 (3.8%)	2936 (3.5%)	3351 (3.3%)
Mean number of tests per person	3.0 ± 1.6	3.0 ± 1.6	2.9 ± 1.6	2.9 ± 1.5
Number of patients with:				
More than 8 tests	71	76	109	129

Trends in HbA_{1c} testing patterns over time from 2006 to 2013 are presented in Table 2.4. The number of repeat tests within 60 days as a proportion of all tests, changed very little over the 10 years; however the proportion of tests taking place more than 366 days from the previous test did increase over time. When these were stratified by previous HbA_{1c}, there was a significant trend in those with less controlled diabetes (>6.5% and >7.5% HbA_{1c}) towards a lower proportion of tests taking place more than a year from the

previous test over time ($p<0.0001$). The mean number of HbA_{1c} tests per person for each two-year interval did not vary from 2006 to 2013.

The number of repeat tests within 60 days or more than 366 days from the previous test varied widely by GP practice. It ranged from one test (in a practice with one patient included in the analysis) to 2845 tests (in a practice with 1356 patients included in the analysis) within a single practice over the 10 year period (results not shown). The percentage of repeat tests taking place within 60 days was 6.8% for the 29 GP practices situated inside the Oxford ring road and 6.2% for the 77 practices outside the Oxford ring road. The percentage of tests carried out more than a year from the previous test was also higher (13.8%) for those within the Oxford ring road than those outside the ring road (11.1% of repeat tests).

The multivariate mixed effects logistic regression models found that older age, testing between December and March, a previous $HbA_{1c}>7.5\%$ and an increase in HbA_{1c} between the previous two measurements were significantly associated with increased odds of re-testing HbA_{1c} within 60 days of the previous test (Table 2.5). Increasing year of test was significantly associated fewer tests within 60 days.

Female sex and year of test were significantly associated with more tests being performed more than a year from the previous test. Older age and previous HbA_{1c} over 7.5% were significantly associated with lower odds of testing more than a year from the previous test (Table 2.5).

For both outcomes, there were some inconsistencies between the univariate and the multivariate analyses. Odds ratio for age was found to change direction between the univariate and multivariate analyses; this was observed both for testing within 60 days and for testing more than a year. When change in effect direction was explored further, it was

not found to be associated with inclusion of any single variable in the model. However, inclusion of two variables, having a previous HbA_{1c} above 7.5% and increase in HbA_{1c} between the previous two measurements, caused the odds ratio for age to change direction in the analysis. In addition to this, two variables which were not significant in the univariate analysis became significant in the multivariate analysis model for re-testing within 60 days (female sex and location of GP practice within the Oxford ring road). Although this was explored, no single factor was found to change this result.

The results from the sensitivity analysis are shown in Table 2.6. These are consistent with the main analysis for all variables, but some of the odds ratios were not significant due to the smaller sample size.

The effect of increasing the number of integration points from 7 points up to 30 points in the univariate analyses and the fully fitted multivariate analysis did not result in any differences in the odds ratio. Results from testing the hierarchical models showed that the AIC and BIC values in the three-level models were smaller than those for the two-level model for both outcomes (Table 2.7); this suggests the three-level model better fits the data (15). These results provide evidence that there are differences in HbA_{1c} testing behaviours between GP practices and it is therefore appropriate to use the three-level model.

Table 2.5 – Logistic regression analysis of factors associated with testing intervals <60 days or >366 days using mixed effects 3-level multilevel model.

	Re-testing HbA_{1c} within 60 days				Re-testing HbA_{1c} >366 days			
	Odds ratio (95%CI)				Odds ratio (95%CI)			
	Univariate	p	Multivariate	p	Univariate	p	Multivariate	p
Age (per year increase)	0.998 (0.997-1.000)	0.006	1.004 (1.003-1.005)	<0.0001	1.004 (1.003-1.005)	<0.0001	0.993 (0.992-0.994)	<0.0001
Sex (female)	1.029 (0.996 – 1.063)	0.087	1.061 (1.022-1.102)	0.002	1.059 (1.029-1.090)	<0.0001	1.068 (1.027-1.115)	0.001
QOF (test Dec-Mar versus rest of year)	1.084 (1.054 – 1.114)	<0.0001	1.099 (1.065-1.134)	<0.0001	0.947 (0.926-0.968)	<0.0001	0.994 (0.967-1.021)	0.651
GP practice location (inside Oxford ring road versus outside ring road)	1.106 (0.957 – 1.279)	0.173	1.209 (1.038-1.410)	0.015	1.173 (0.950-1.448)	0.138	1.279 (0.994-1.644)	0.056
Previous HbA_{1c}>7.5% versus ≤7.5%	2.736 (2.657-2.818)	<0.0001	2.155 (2.083-2.229)	<0.0001	0.674 (0.656-0.692)	<0.0001	0.468 (0.452-0.485)	<0.0001
Increase in HbA_{1c} (in %) between previous two measures	1.119 (1.104-1.135)	<0.0001	1.044 (1.029-1.058)	<0.0001	0.949 (0.938-0.960)	<0.0001	1.001 (0.989-1.014)	0.851
Increasing year of test	0.997 (0.992 – 1.002)	0.260	0.964 (0.958-0.970)	<0.0001	1.163 (1.159-1.168)	<0.0001	1.114 (1.108-1.120)	<0.0001

Table 2.6 - Sensitivity analysis using a random 2 measurements for each patient without baseline HbA_{1c} or previous HbA_{1c}.

	Re-testing HbA_{1c} within 60 days				Re-testing HbA_{1c} >366 days			
	Odds ratio (95%CI)				Odds ratio (95%CI)			
	Univariate	p	Multivariate	p	Univariate	p	Multivariate	p
Age (per year increase)	0.992 (0.990 - 0.994)	<0.0001	1.002 (0.999-1.005)	0.203	0.999 (0.998-1.000)	0.221	0.998 (0.996-0.999)	0.043
Sex (female)	1.009 (0.944-1.079)	0.791	1.045 (0.952-1.146)	0.358	1.093 (1.049-1.140)	<0.0001	1.041 (0.980-1.106)	0.197
QOF (test Dec-Mar versus rest of year)	1.076 (1.002-1.156)	0.044	1.033 (0.936-1.140)	0.518	0.983 (0.939-1.028)	0.446	0.979 (0.918-1.045)	0.526
GP practice location (inside Oxford ring road versus outside ring road)	1.057 (0.891-1.255)	0.523	1.228 (1.216-1.475)	0.029	1.340 (1.103-1.627)	0.003	1.286 (1.008-1.641)	0.043
Previous HbA_{1c}>7.5% versus ≤7.5%	1.703 (1.586-1.828)	<0.0001	1.886 (1.709-2.081)	<0.0001	0.439 (0.415-0.464)	<0.0001	0.523 (0.486-0.563)	<0.0001
Increase in HbA_{1c} (in %) between previous two measures	1.126 (1.078-1.174)	<0.0001	1.061 (1.019-1.104)	0.004	0.965 (0.940-0.991)	0.010	1.004 (0.975-1.034)	0.777
Increasing year of test	0.970 (0.958-0.982)	<0.0001	0.963 (0.946-0.980)	<0.0001	1.134 (1.124-1.143)	<0.0001	1.127 (1.112-1.141)	<0.0001

Table 2.7 - Testing hierarchical model fit using AIC and BIC.

	AIC	BIC
<60 days : 2-level model	0	0
<60 days : 3-level model	-903	-893
>366 days : 2-level model	0	0
>366 days : 3-level model	-4069	-4058

2.2.3 Discussion

This analysis has several limitations. These include not being able to definitively establish whether patients in the dataset had a diagnosis of diabetes, not being able to differentiate type of diabetes and not being able to explore the impact of medications or co-morbidities on HbA_{1c} testing. It was likely that some patients included in the analysis did not have diabetes; this could have biased the findings, particularly those for long testing intervals. Furthermore, some patients in this analysis may have had other indications which exempted them from inclusion in QOF reporting or justified more frequent HbA_{1c} testing. These could not be explored further because there was insufficient information on comorbidities and medication use.

It was therefore not possible to draw conclusions from this hospital laboratory dataset; instead this has been used as a methodological exercise to develop statistical models and to develop a hypothesis on which to base a more thorough analysis using CPRD data. The work helped to inform a protocol in application for a larger CPRD dataset described in the next section.

2.3 HbA_{1c} test requests in diabetes patients across the UK

2.3.1 Introduction

I will now extend the previous analysis to establish whether more frequent HbA_{1c} testing in the months prior to QOF is also observed in national data. This will allow me to examine these associations more comprehensively by having (i) a larger sample size, (ii) a cohort with diagnosed diabetes and (iii) access to larger geographic spread and more information on patient-level data. Because there may be differences in HbA_{1c} testing between England, Scotland and Wales, or differences between testing rates in London and the South of England compared with the North of England, I would like to explore potential associations between testing frequency and geographic location; I will also examine the impact of medication use and differences between insulin and non-insulin users.

Research question: is there an association between patients' HbA_{1c} testing frequency with time of year (relative to QOF dates) and previous HbA_{1c} levels in people with diabetes?

2.3.2 Methods

After review by a patient representative, the protocol was submitted to the Independent Scientific Advisory Committee (ISAC) and approved in May 2015 (ISAC Protocol 15_099, see Appendix 1.2). Data from 100,000 patients with a diagnosis of diabetes from GP practices across the UK registered with the Clinical Practice Research Datalink (CPRD) were sought.

Inclusion criteria:

Adults (≥18 years) with a diagnosis of diabetes were included. Diabetes diagnosis could be pre-existing or take place at any point between 1st January 2005 and 31st December 2014.

In patients with existing diabetes, the index HbA_{1c} test was defined as the first HbA_{1c} test after 1st January 2005; included patients must have had a minimum of two HbA_{1c} tests prior to the index test date and post-diagnosis. Patients with incident diabetes over the 10 years follow up from Jan 2005 to Dec 2014 were included; these patients must have had a minimum of three HbA_{1c} test results post diagnosis, and the second HbA_{1c} test was defined as the index test date in these patients.

Exclusion criteria:

- Ambiguously recorded gender.
- Patients with gestational diabetes, malnutrition-related diabetes, maturity onset diabetes of the young (MODY), bronzed diabetes or steroid-induced diabetes.
- Patients with fewer than three HbA_{1c} measures in total.
- Patients with cancer or end-stage renal disease.

Sample size calculation

In a cohort of 100,000 diabetes patients with multiple HbA_{1c} measures, it was estimated that 10% would have type 1 diabetes (16). Of the remaining 90,000 with type 2 diabetes, around 15% would be insulin users (16). This would leave over 75,000 patients with type 2 diabetes who are non-insulin users, but would still allow separate analysis of insulin users and of the full dataset. The main analysis is to examine whether re-testing HbA_{1c} within 60 days is more frequent between the months of December and March (Dec-Mar) compared with April to November: assuming that each patient has a mean of 8 tests over the 10 years (based on data from John Radcliffe hospital laboratory dataset). This would give a total of 400,000 HbA_{1c} tests in non-insulin users, 325,000 of which would be repeat tests. If only 2% of tests were repeated within 60 days (a conservative estimate), this would equate to 7000. Initial results from the hospital dataset gave an odds ratio for

testing Dec-Mar of 1.12, and 95% confidence intervals for the odds ratio in the CPRD dataset were estimated to be 1.07 to 1.18; this would be sufficient to detect a significant odds ratio if this group were to be separately analysed.

Data Management:

The data cut used CPRD Gold data. Diabetes product and medical code lists which had been validated in previous research (17) were used (Appendix 1). Data cleaning and some data management were carried out by members of the CPRD team at the Nuffield Department of Primary Care Health Sciences in Oxford:

Type 2 diabetes was recorded for those with a medical code for type 2 diabetes any time before test index date, type 1 diabetes recorded for those with a medical code for type 1 diabetes any time before test index date. A few people had medical codes for both type 1 and type 2 diabetes, which were not changed for the dataset (1.3% of total), and 7.1% had no code specific to type 1 or type 2 diabetes code recorded before test index date. A list of medical codes is provided in Appendix 1. Age was set as the age of the patient at the index test date. For covariates which could change over time such as body mass index (BMI), total cholesterol or systolic blood pressure, the closest value from up to two years prior to the index test date was used, and cases in which no values are available within this time frame were treated as missing data. Use of lipid-lowering or antihypertensive medications were set at baseline levels. Those with a diagnosis of microalbuminuria at or prior to their index test date were coded as having microalbuminuria.

Patients were coded as receiving lipid-lowering medication or antihypertensive medication for the duration of follow-up if they had a product code for these at any time prior to index test date.

Gender was coded: 1=male, 2=female.

Smoking status was coded as 1=non-smoker, 2=ex-smoker or 3=current-smoker. Missing data on smoking were re-coded as non-smoker (18).

Type of diabetes was coded as 1=type1 and 2=type2.

Patients remained in the analysis until the end of follow-up on 31st December 2014 or when they left the surgery, died, or developed cancer or end-stage renal disease.

I carried out all remaining data management myself, including coding of diabetes medications, geographic region of the UK and merging of datasets on medication, HbA_{1c} test data and patient-related data as detailed below.

Region of the UK in the CPRD are coded as follows (and Figure 2.2):

0	Missing
1	North East
2	North West
3	Yorkshire & The Humber
4	East Midlands
5	West Midlands
6	East of England
7	South West
8	South Central
9	London
10	South East Coast
11	Northern Ireland
12	Scotland
13	Wales

England was divided into the following regions: North (1, 2 & 3), Midlands & East (4, 5 & 6), South & West (7 & 8) and London & SE (9 & 10).

Figure 2.2 - Geographic regions of England used in CPRD data.



Diabetes medications were grouped into drug classes: SGLT2 inhibitors, DPP4 inhibitors, GLP1 agonists, alpha-glucosidase inhibitors, meglitinide, sulphonylureas, thiazolidinediones, metformin or insulin. A medication change was defined as prescription of any new type of diabetes medication (or drug class) at or following the previous HbA_{1c} test. Thus, a new variable was created and coded as 1 or 0 at each HbA_{1c} test date to flag up whether there had been *addition* of a new diabetes medication since the previous visit. Because of unexpected findings in the analysis, a second variable was created to flag up a medication change prior to the previous HbA_{1c} test. This was then included in a *post-hoc* analysis. Diabetes medication type was coded for each patient as 'no medication prescription', 'oral', 'insulin' or 'both' oral- and insulin-treated, based on the medication that was prescribed most frequently for that patient. Injectable non-insulin medications such as exenatide were categorised as 'oral' medication rather than insulin. Data on patient characteristics, medication use and HbA1c test data were merged so that multiple rows were available for each HbA_{1c} result, test date and recent medication change for each

patient. Change in HbA_{1c} was defined as the change between the previous HbA_{1c} (n−1) and the HbA_{1c} test result prior to that (n−2).

Post-hoc analyses recommended by DPhil examiners were carried out to explore how testing patterns may be affected by old age and by incident diabetes. Age of patients was dichotomised to those 80 years and under and those over 80 years; it was included as a covariate in both models. Incident diabetes was coded as those whose diagnosis was recorded after 1st January 2005.

1. Descriptive analysis

Descriptive data on patient age, sex, types of diabetes medication, BMI, systolic blood pressure, mean number of tests per patient, mean HbA_{1c} at index date, mean testing interval and numbers of tests less than 60 days or more than 366 days from the previous test were tabulated for all patients and for subgroups stratified by sex, type of diabetes and insulin use. The number of tests performed each year and the mean number of test requests for each month of the 10-year follow-up were presented graphically in bar charts. Numbers of HbA_{1c} tests taking place at different time intervals from the previous test were tabulated within subgroups of patients categorised by the previous HbA_{1c} test result: patients with HbA_{1c}<6.5% were defined as tightly controlled diabetes, patients with HbA_{1c}≥6.5% and <7.5% were defined as having well controlled diabetes, and patients with HbA_{1c}≥7.5% as uncontrolled diabetes. The total numbers of tests performed and numbers taking place <60 days or >366 days from the previous test in 2-year periods throughout the 10 years from 2007 to 2014 were reported so that trends over time could be explored.

Comparison of the rate of HbA_{1c} testing between those with type 1 and type 2 diabetes was tabulated, as well as testing rates between different geographic location (England, Scotland, Wales and different regions of the England).

2. Multi-level logistic regression models

The analyses were carried out on the whole cohort of included patients, and separately for those with type 1 and type 2 diabetes. Univariate and multivariate analyses were conducted in the 10 years of patient data from 1st January 2005 to 31st December 2014: a three-level mixed effects model was used to account for multiple measures in each patient nested within each GP practice.

(i) In a hypothesis-testing analysis, univariate and stepwise multivariate logistic regression was used to examine (a) whether patient-level and (b) GP practice-level factors were associated with HbA_{1c} testing intervals <60 day (or >366 days) from the previous test. The relationships between time of year (Dec-Mar versus Apr-Nov) and previous HbA_{1c}>7.5% (or 58 mmol/mol) compared with HbA_{1c}≥7.5% were reported as odds ratios and 95% confidence intervals (CI).

(ii) In a hypothesis-generating analysis, patient and GP practice-level factors were examined and their association with re-testing HbA_{1c} at <60 day (or >366 day) test intervals reported as odds ratios (OR) and 95% confidence intervals (95% CI). Candidate exposure variables examined were:

- Increasing year of age;
- Female sex compared with male;
- Absolute change in HbA_{1c} between the two previous measures;
- Increasing year of test;
- Increasing baseline BMI;
- Increasing blood pressure and total cholesterol measures;
- Smoking status (ex-smoker or current smoker compared with non-smoker);

- Diagnosis of microalbuminuria or nephropathy compared with no diagnosis;
- Type of diabetes (type 2 relative to type 1);
- Medication change at previous visit compared with no medication change;
- Prescription for lipid-lowering or antihypertensive medication (as a proxy for existence of comorbidities) compared with no prescription for these medications;
- GP practice, geographic regions (Scotland, Wales, England, and regionally within England);
- Medications taken (where appropriate – no medication prescription, insulin, oral medications or both); and
- Recent medication change compared with no medication change.

A *p* value of <0.05 was considered to be significant. The *runiform* command in Stata was used to randomly order the HbA_{1c} results and one test result was selected for each patient. A sensitivity analysis was carried out for each of the analyses using a two-level logistic regression model based on the time interval for the randomly selected HbA_{1c} measurement for each patient, to ensure that results were robust.

Statistical methods

The fit of logistic regression models was tested using the likelihood ratio test and AIC and BIC. Smaller AIC and BIC values indicate a better-fitting model (15). The inter-class correlation coefficient was calculated using the command "estat icc" in Stata to calculate the amount of variance which could be ascribed to the patient and practice level. Any inconsistencies in the data were explored by re-testing the models using a step-wise approach, and removing variables which exhibited collinearity between each other.

The effect of increasing the number of integration points for each level of random effects was tested by increasing from the default 7 points up to 50 points in the univariate and multivariate analyses. The more integration points, the more accurate the approximation to the log likelihood.

2.3.3 Results

Results from descriptive analysis

Characteristics of the cohort are presented in Table 2.8. The cohort of 100,000 patients had a total of 953,634 HbA_{1c} tests over the 10 years of follow up. Mean age of patients was 63.4 years, 44.7% were female, mean BMI was 30.6 kg/m^2, 86,495 had type 2 diabetes, 6208 had type 1 diabetes, and 7297 patients had unknown diabetes status. Just over 25% of all patients (25,943) were insulin users (8521 of whom used insulin alone and 17,422 of whom used both insulin and oral medications during follow-up) 57,396 patients were prescribed oral medications and 16,661 patients had no record of medication prescriptions for their diabetes. The mean year of diabetes diagnosis was 2005 (range 1988 to 2014) and mean follow-up in the dataset was 1704 days equating to 4 years and 8 months. Mean HbA_{1c} at index date was higher in insulin (8.47%, 69 mmol/mol) compared with non-insulin users (7.07%, 54 mmol/mol). The numbers of HbA_{1c} tests performed each year between 2005 and 2014 are shown in Figure 2.3a, there was a slight increase in the total number of HbA_{1c} tests each year from 2005 to 2011, and thereafter a slight decrease from 2011 to 2014. The number of HbA_{1c} tests performed in each month of the year is shown in Figure 2.3b, there are slightly fewer tests performed in April, August and December.

Table 2.9 shows the numbers of tests carried out at different test intervals, stratified by subgroup of previous HbA_{1c}. Over the 10 years of the cohort follow-up, there were a total of 868,847 repeat tests, of which 74,650 tests (8.6% of all tests) were carried out within 60 days of the previous test. Of these, 27,813 were in patients with a previous HbA_{1c} below 7.5% (58 mmol/mol). There were 81,949 tests (9.4% of all tests) carried out more than a year from the previous test, of which 26,117 were carried out in those with a previous HbA_{1c} above 7.5% (58 mmol/mol).

Table 2.8 - CPRD cohort characteristics.

	Total number (n)	Age	% Female	BMI (kg/m^2)	SBP (mm Hg)	Mean number of tests/ patient	Mean HbA_{1c} at index (%)	Mean test interval (days)	Number of test<60 days (%)	Number of tests>366 days (%)
Total dataset	100,000	63.4±14.3	44.7%	30.6±6.5	135.7±16.6	8.9±6.9	7.44±1.31	191.7±134.5	83,496 (9.4%)	83,579 (9.4%)
Females	44,655	64.8±14.9	-	31.3±7.2	136.1±17.2	8.9±6.9	7.41±1.33	191.5±134.9	37,848 (9.6%)	37,093 (9.4%)
Males	55,345	62.2±13.6	-	30.1±5.8	135.4±16.0	9.0±6.8	7.47±1.30	191.8±134.1	45,648 (9.2%)	46,486 (9.4%)
Type 1 diabetes	6208	43.0±16.2	42.8%	27.0±5.3	128.8±17.0	9.3±7.1	8.64±1.75	203.2±164.9	6503 (12.0%)	6701 (12.3%)
Type 2 diabetes	86,495	64.8±12.9	44.5%	30.9±6.4	136.1±16.4	9.1±6.8	7.41±1.26	189.4±126.0	71,418 (9.0%)	70,429 (8.9%)
Unknown diabetes type	7297	64.5±14.1	48.5%	30.6±6.7	136.3±17.1	6.3±6.1	7.23±1.43	217.7±209.5	4253 (9.6%)	5983 (13.6%)
Insulin use	25,943	56.8±16.2	44.9%	30.5±7.0	134.4±17.6	11.5±7.9	8.47±1.75	182.2±148.1	39,804 (12.5%)	27,600 (8.7%)
No insulin	74,057	65.7±12.7	44.6%	30.7±6.3	136.2±16.2	8.0±6.2	7.07±1.32	206.8±171.9	47,999 (7.3%)	72,535 (11.0%)

Table 2.10 shows the number of HbA_{1c} tests performed outside the recommended testing intervals, presented in two-yearly intervals. More HbA_{1c} tests took place in 2011-2012 than in any other two-year interval. There was a trend towards the proportion of tests taking place within 60 days of the previous test decreasing over time. For each 2-year interval there was an increase in the proportion of tests taking place more than a year from the previous test from 2007/8 to 2013/14, and an increase in the proportion taking place more than 15 months (455 days) from the previous test. However, of these, the proportion with a previous HbA_{1c} above 7.5% (58mmol/mol) was small (≤4.1%). The number of patients with more than 8 tests in each 2-year period decreased over time.

Figure 2.3 – Number of HbA_{1c} tests per year and per month in CPRD cohort.

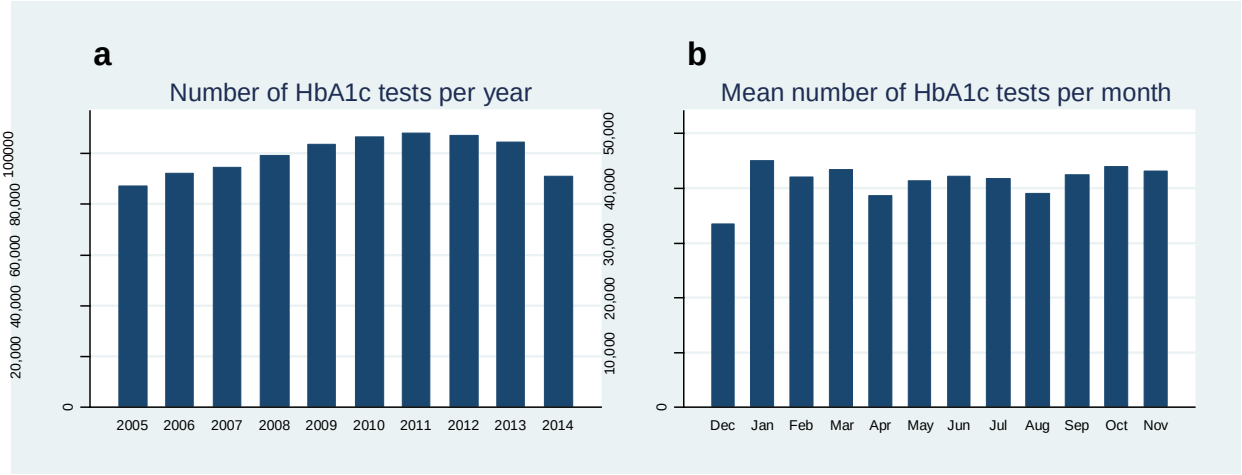


Table 2.9 – Number of tests carried out at different test intervals, stratified by subgroup of previous HbA_{1c}.

	Test Interval (days)							
Previous HbA_{1c}	**<60**	**60-89**	**90-119**	**120-179**	**180-365**	**>366**	**Total**	**Median (IQR) test interval (days)**
All tests	74,650	75,469	115,308	194,159	326,283	81,949	867,818	172 (101, 245)
<6.5	9877	8958	14,482	39,453	87,128	26,947	186,845	197 (147, 316)
6.5-7.5	17,866	19,044	32,636	69,317	129,405	29,311	297,579	183 (123, 253)
7.5-10	31,557	36,742	55,152	68,599	87,593	19,370	299,013	141 (91, 211)
≥10	15,280	10,725	13,038	16,790	22,157	6977	84,967	151 (86, 238)

Table 2.10 – Repeat HbA_{1c} testing within 60 days and more than 366 days from the previous test in two-yearly intervals in CPRD cohort.

	2007-2008	2009-2010	2011-2012	2013-2014
Number of patients	68,457	72,728	72,271	62,419
Total number of tests	190,848	201,651	206,345	191,492
Total number of repeat tests	177,316	188,432	193,929	183,724
Tests<60 days	15,796 (8.9%)	15,051 (8.0%)	13,297 (6.8%)	13,377 (7.3%)
Tests>366 days	16,447 (9.3%)	19,168 (10.2%)	20,573 (10.6%)	20,371 (11.1%)
Tests>366 days & previous HbA_{1c}>6.5%	10,564 (6.0%)	11,974 (6.4%)	13,597 (7.0%)	13,380 (7.3%)
Tests>366 days & previous HbA_{1c}>7.5%	5068 (2.9%)	5558 (2.9%)	6327 (3.3%)	6462 (3.5%)
Tests>455 days	5398 (3.0%)	6903 (3.6%)	7491 (3.9%)	7448 (4.1%)
Number of patients with:				
More than 8 tests	575	463	428	340

The rate of HbA_{1c} testing was tabulated as mean number of tests per person and mean number of tests per person per year stratified by type of diabetes and region of the UK (Table 2.11). Those with type 1 and type 2 diabetes had similar rates of HbA_{1c} testing. Those in Scotland and Northern Ireland had significantly higher rates of testing than all other parts of the UK. London and the Midlands and East of England had the lowest rates of testing in the UK.

Table 2.11 - Rate of HbA_{1c} testing.

	Mean (± SD) number of tests per person	Mean number of tests per person per year
Type 1 diabetes	10.3 ± 7.2	1.51 ± 0.47
Type 2 diabetes	10.1 ± 6.8	1.53 ± 0.45
By region:		
North of England	9.8 ± 6.7	1.51 ± 0.45
Midlands & east England	9.3 ± 6.5	1.50 ± 0.44
South & west England	10.0 ± 6.8	1.52 ± 0.44
London & SE England	9.3 ± 6.4	1.47 ± 0.42
Northern Ireland	11.5 ± 7.7	1.60 ± 0.49
Scotland	11.6 ± 8.0	1.63 ± 0.52
Wales	10.5 ± 7.0	1.52 ± 0.44

Hierarchical models

Testing between December and March and previous HbA_{1c}>7.5%

Results from the three-level logistic regression models for the whole cohort and separately for type 1 and type 2 diabetes are shown in Table 2.12. Both pre-specified primary variables of HbA_{1c} test date between December and March and having a previous HbA_{1c} above 7.5% (58 mmol/mol) were found to have a significant influence on HbA_{1c} testing behaviour irrespective of type of diabetes.

Short testing interval (<60 days)

Results from the univariate analysis found that overall people who have their HbA_{1c} tested between December and March had significantly higher odds of having an HbA_{1c} test within the previous 60 days than people tested in other months of the year (OR 1.06, 95% CI 1.05-1.08, p<0.0001) (Table 2.12). The univariate analysis also showed that those whose previous HbA_{1c} was above 7.5% had significantly higher odds of receiving a repeat HbA_{1c} test within 60 days compared with those with lower HbA_{1c} (OR 2.21, 95% CI 2.18-2.25, p<0.0001). Including both variables in the analysis gave similar results (OR for testing in Dec-Mar versus Apr-Nov 1.06, 95% CI 1.04-1.08, and OR for previous HbA_{1c}>7.5% versus lower HbA_{1c} 2.21, 95% CI 2.18-2.25). The results were similar after adjustment for all pre-defined covariates in the multivariate analysis (Table 2.13). When analysed separately for those with type 2 diabetes, results were similar (Table 2.14). The sensitivity analysis in which a single random test was used for each patient is shown in Table 2.15; results from this are similar to the main analysis, though time of year was no longer significant due to the smaller sample size.

Long testing interval (>366 days)

Those who had their HbA_{1c} tested between December and March had a significantly higher odds of their test being longer than 366 days from their previous test compared with those who were tested at other times of year (OR 1.07, 95% CI 1.05-1.08, p<0.0001) (Table 2.12). Those with a previous HbA_{1c} of 7.5% or above were significantly less likely to have had an HbA_{1c} test more than a year from the previous test compared with those with lower HbA_{1c} (OR 0.48, 95% CI 0.47-0.49, p<0.0001). Results when both variables were included in the analysis were similar (OR for testing in Dec-Mar versus Apr-Nov 1.07, 95% CI 1.06-1.09, and OR for previous HbA_{1c}>7.5% versus lower HbA_{1c} 0.45, 95% CI 0.47-0.49). The results were similar after adjustment for all pre-defined covariates in the multivariate analysis (Table 2.13). Results for those with type 2 diabetes only were similar (Table 2.14). The sensitivity analysis in which a single random test was used for each patient is shown in Table 2.15; results from this are similar to the main analysis.

Multivariate analysis including all pre-defined covariates

Short testing interval (<60 days)

When including all pre-defined covariates in the model, I found the following to be significantly associated with increased odds of re-testing HbA_{1c} within 60 days: testing between December and March compared with other months of the year, having a previous HbA_{1c}>7.5% compared with a lower HbA_{1c}, increasing year of age, increase in BMI, a diagnosis of microalbuminuria compared with no diagnosis, having type 2 diabetes compared with type 1 diabetes, taking lipid-lowering or antihypertensive drugs compared with taking no medications, living in Northern Ireland or Scotland compared to the North of England or taking oral and/or insulin treatment compared to no medication prescription (Table 2.13).

More recent test year, increasing systolic blood pressure, having had a recent medication change compared with no change and location in the Midlands or East of England, South and West of England or London and the South East compared with the North of England, were all significantly associated with lower odds of re-testing HbA_{1c} within 60 days (Table 2.13).

Results for those with type 2 diabetes only are presented in Table 2.14; the findings from the multivariate analysis were consistent and similar to the main analysis. The sensitivity analysis using a random measurement from each patient in the cohort gave results which were consistent with the full analysis, but with fewer significant findings (Table 2.15).

The *post-hoc* re-coding of medication change to a change in medication immediately prior to the previous HbA_{1c} test gave an odds ratio of 1.17 (95% CI 1.15-1.19) compared to no medication change. The analysis of older age found that people over 80 years were more likely to have their HbA1c re-tested within 60 days OR 1.17 (95% CI 1.13 to 1.21) compared with those 80 years and under. Comparison of those who developed diabetes during follow-up (incident diabetes) with those with existing diabetes found they were less likely to have their HbA_{1c} re-tested within 60 days (OR 0.90, 95% CI 0.89 to 0.92).

Long testing interval (>366 days)

When including all pre-defined covariates in the model, I found the following to be significantly associated with higher odds of re-testing HbA_{1c} more than a year from the previous test: testing between December and March compared with other months of the year, an increase in HbA_{1c} between the previous two measurements, increasing test year, increasing BMI, increasing systolic blood pressure, increasing total cholesterol, being a current smoker compared to non-smokers, having a diagnosis of microalbuminuria compared with no diagnosis, having had a recent medication change compared to no

change in medication, and GP practice location in London or the South-east of England, compared to the North of England (Table 2.13).

A previous HbA_{1c} above 7.5% compared with a lower HbA_{1c}, increasing age, having type 2 diabetes relative to type 1 diabetes, taking lipid-lowering or antihypertensive medication compared with taking no medications, GP practice location in Scotland compared with North of England and taking oral and/or insulin treatment compared with no medication prescription were all significantly associated with a lower odds of re-testing HbA_{1c} more than a year from the previous test (Table 2.13).

Results for those with type 2 diabetes only are presented in Table 2.14; the findings from the multivariate analysis were consistent with and similar to the main analysis. The sensitivity analysis using a random measurement from each patient in the cohort gave results which were consistent with the full analysis, but with fewer significant findings (Table 2.15).

The *post-hoc* re-coding of recent medication change to a change in medication immediately prior to the previous HbA_{1c} test gave an odds ratio of 0.77 (95% CI 0.76-0.79) compared to no medication change. The analysis of older age found that people over 80 years were more likely to have more than a year between their HbA1c tests compared with those 80 years and under, (OR 1.32, 95% CI 1.27 to 1.37). Comparison of those who developed diabetes during follow-up (incident diabetes) with those with existing diabetes found they were less likely to have their HbA_{1c} re-tested more than a year from the previous test (OR 0.74, 95% CI 0.72 to 0.75).

Table 2.12 - Logistic regression analysis of whether testing between December and March and having a previous HbA_{1c} greater than 7.5% are associated with testing intervals <60 days or >366 days from the previous test.

	<60 days				**>366 days**			
	Odds ratio (95%CI)				**Odds ratio (95%CI)**			
	Univariate	**p**	**Multivariate**	**p**	**Univariate**	**p**	**Multivariate**	**p**
All patients								
QOF (test Dec-Mar versus rest of year)	1.064 (1.048-1.081)	<0.0001	1.059 (1.043-1.076)	<0.0001	1.065 (1.048-1.082)	<0.0001	1.072 (1.056-1.089)	<0.0001
Previous HbA1>7.5% versus ≤7.5%	2.214 (2.179-2.250)	<0.0001	2.213 (2.178-2.249)	<0.0001	0.478 (0.470-0.487)	<0.0001	0.448 (0.469-0.487)	<0.0001
Type 1 diabetes only								
QOF (test Dec-Mar versus rest of year)	1.048 (1.006-1.092)	0.024	1.044 (1.002-1.087)	0.039	1.079 (1.037-1.122)	<0.0001	1.084 (1.042-1.128)	<0.0001
Previous HbA1>7.5% versus ≤7.5%	1.576 (1.505-1.649)	<0.0001	1.575 (1.505-1.648)	<0.0001	0.559 (0.533-0.586)	<0.0001	0.558 (0.533-0.585)	<0.0001
Type 2 diabetes only								
QOF (test Dec-Mar versus rest of year)	1.063 (1.046-1.080)	<0.0001	1.058 (1.041-1.075)	<0.0001	1.060 (1.043-1.078)	<0.0001	1.069 (1.051-1.087)	<0.0001
Previous HbA1>7.5% versus ≤7.5%	2.289 (2.251-2.328)	<0.0001	2.288 (2.250-2.327)	<0.0001	0.428 (0.420-0.436)	<0.0001	0.428 (0.419-0.436)	<0.0001

Table 2.13 - Logistic regression analysis of whether covariate factors are associated with testing intervals <60 days or >366 days from the previous test.

	<60 days		**>366 days**	
	Odds ratio (95%CI)		**Odds ratio (95%CI)**	
	Multivariate	**p**	**Multivariate**	**p**
QOF (test Dec-Mar versus rest of year)	1.057 (1.038-1.077)	<0.0001	1.053 (1.133-1.072)	<0.0001
Previous HbA1>7.5% versus ≤7.5%	2.001 (1.959-2.044)	<0.0001	0.459 (0.448-0.470)	<0.0001
Age (years)	1.006 (1.005-1.007)	<0.0001	0.993 (0.992-0.994)	<0.0001
Sex (female versus male)	1.013 (0.991-1.036)	0.256	0.998 (0.973-1.023)	0.871
Change in HbA_{1c} between previous two measurements (%)	0.999 (0.991-1.007)	0.791	1.022 (1.013-1.031)	<0.0001
Increasing year of test	0.968 (0.965-0.971)	<0.0001	1.042 (1.038-1.046)	<0.0001
Increasing baseline BMI (kg/m^2)	1.006 (1.004-1.008)	<0.0001	1.003 (1.000-1.005)	0.017
Increasing systolic blood pressure (mmHg)	0.999 (0.998-1.000)	<0.0001	1.005 (1.004-1.006)	<0.0001
Increasing total cholesterol (mmol/l)	0.996 (0.990-1.003)	0.246	1.014 (1.009-1.020)	<0.0001
Smoking status	Reference non-smoker Ex-smoker: 0.990 (0.964-1.017) Current: 0.980 (0.947-1.014)	 0.463 0.244	Reference non-smoker Ex-smoker: 0.985 (0.956-1.015) Current: 1.254 (1.208-1.302)	 0.328 <0.0001
Diagnosis of micro-albuminuria versus no diagnosis	1.145 (1.102-1.189)	<0.0001	1.049 (1.001-1.100)	0.044
Type of diabetes	Type 1 reference Type 2: 1.060 (1.001-1.122)	0.046	Type 1 reference Type 2: 0.634 (0.590-0.681)	<0.0001
Recent medication change versus no medication change	0.342 (0.333-0.350)	<0.0001	1.175 (1.147-1.205)	<0.0001
Taking lipid lowering or anti-hypertensives versus no medications	1.067 (1.027-1.108)	0.001	0.854 (0.820-0.890)	<0.0001
Geographic region of GP practice	Inclusion of region in model	<0.0001	Inclusion of region in model	<0.0001
Diabetes treatment	Reference= no medication prescription **Oral** 1.674 (1.599-1.752) **Insulin** 2.259 (2.116-2.411) **Both** 3.501 (3.327-3.685)	 <0.0001 <0.0001 <0.0001	Reference= no medication prescription **Oral** 0.548 (0.528-0.569) **Insulin** 0.767 (0.715-0.824) **Both** 0.452 (0.431-0.475)	 <0.0001 <0.0001 <0.0001

Table 2.14 - Logistic regression analysis of whether covariate factors are associated with testing intervals <60 days or >366 days from the previous test in type 2 diabetes only.

	<60 days		**>366 days**	
	Odds ratio (95%CI)		**Odds ratio (95%CI)**	
	Multivariate	**p**	**Multivariate**	**p**
QOF (test Dec-Mar versus rest of year)	1.056 (1.036-1.077)	<0.0001	1.050 (1.030-1.071)	<0.0001
Previous HbA1>7.5% versus ≤7.5%	2.086 (2.040-2.132)	<0.0001	0.435 (0.424-0.446)	<0.0001
Age (years)	1.007 (1.006-1.008)	<0.0001	0.995 (0.993-0.996)	<0.0001
Sex (female versus male)	0.995 (0.972-1.019)	0.698	1.006 (0.980-1.032)	0.673
Change in HbA_{1c} between previous two measurements (%)	1.000 (0.991-1.008)	0.938	1.025 (1.016-1.034)	<0.0001
Increasing year of test	0.968 (0.965-0.971)	<0.0001	1.043 (1.039-1.046)	<0.0001
Increasing baseline BMI (kg/m^2)	1.007 (1.005-1.009)	<0.0001	1.003 (1.001-1.005)	0.007
Increasing systolic blood pressure (mmHg)	0.999 (0.998-1.000)	0.003	1.005 (1.004-1.006)	<0.0001
Increasing total cholesterol (mmol/l)	0.998 (0.992-1.004)	0.538	1.013 (1.008-1.019)	<0.0001
Smoking status	Reference non-smoker Ex-smoker: 0.990 (0.963-1.017) Current: 0.985 (0.951-1.020)	 0.456 0.396	Reference non-smoker Ex-smoker: 0.977 (0.948-1.008) Current: 1.242 (1.195-1.292)	 0.144 <0.0001
Diagnosis of micro-albuminuria versus no diagnosis	1.152 (1.107-1.198)	<0.0001	1.075 (1.024-1.129)	0.003
Type of diabetes	0.342 (0.334-0.351)	<0.0001	1.181 (1.152-1.211)	<0.0001
Recent medication change versus no medication change	1.085 (1.041-1.131)	<0.0001	0.857 (0.821-0.895)	<0.0001
Geographic region of GP practice	Inclusion of region in model	<0.0001	Inclusion of region in model	<0.0001
Diabetes treatment	Reference= no medication prescription **Oral** 1.650 (1.576-1.727) **Insulin** 2.240 (2.087-2.403) **Both** 3.395 (3.225-3.574)	 <0.0001 <0.0001 <0.0001	Reference= no medication prescription **Oral** 0.556 (0.536-0.577) **Insulin** 0.820 (0.758-0.887) **Both** 0.466 (0.444-0.489)	 <0.0001 <0.0001 <0.0001

Table 2.15 - Sensitivity analysis of logistic regression of association of covariate factors with testing intervals <60 days or >366 days from the previous test in type using only a single measurement from each patient in the total cohort.

	<60 days		**>366 days**	
	Odds ratio (95%CI)		**Odds ratio (95%CI)**	
	Multivariate	**p**	**Multivariate**	**p**
QOF (test Dec-Mar versus rest of year)	1.054 (0.993-1.119)	0.086	1.073 (1.024-1.125)	0.003
Previous HbA1>7.5% versus ≤7.5%	1.970 (1.847-2.103)	<0.0001	0.575 (0.543-0610)	<0.0001
Age (years)	1.004 (1.002-1.007)	0.001	0.997 (0.995-0.999)	0.003
Sex (female versus male)	1.024 (0.966-1.085)	0.426	1.036 (0.990-1.084)	0.125
Change in HbA_{1c} between previous two measurements (%)	0.969 (0.945-0.994)	0.016	1.024 (1.001-1.047)	0.040
Increasing year of test	0.927 (0.917-0.936)	<0.0001	1.052 (1.043-1.061)	<0.0001
Increasing baseline BMI (kg/m^2)	1.003 (0.998-1.008)	0.201	1.002 (0.998-1.005)	0.419
Increasing systolic blood pressure (mmHg)	0.997 (0.996-0.999)	0.003	1.004 (1.002-1.005)	<0.0001
Increasing total cholesterol (mmol/l)	0.988 (0.967-1.009)	0.268	1.014 (1.003-1.024)	0.012
Smoking status	Reference non-smoker Ex-smoker: 0.974 (0.910-1.041) Current: 0.948 (0.870-1.032)	 0.436 0.218	Reference non-smoker Ex-smoker: 1.000 (0.948-1.055) Current: 1.244 (1.164-1.329)	 0.992 <0.0001
Diagnosis of micro-albuminuria versus no diagnosis	1.284 (1.170-1.409)	<0.0001	0.954 (0.872-1.044)	0.309
Type of diabetes	Type 1 reference Type 2: 1.105 (0.957-1.275)	0.174	Type 1 reference Type 2: 0.678 (0.591-0.777)	<0.0001
Recent medication change versus no medication change	0.388 (0.358-0.420)	<0.0001	1.149 (1.080-1.223)	<0.0001
Taking lipid lowering or anti-hypertensives versus no medications	1.110 (1.007-1.224)	0.035	0.822 (0.766-0.882)	<0.0001
Geographic region of GP practice	Inclusion of region in model	<0.0001	Inclusion of region in model	<0.0001
Diabetes treatment	Reference= no medication prescription **Oral** 1.550 (1.393-1.726) **Insulin** 2.089 (1.784-2.447) **Both** 3.140 (2.770-3.559)	 <0.0001 <0.0001 <0.0001	Reference= no medication prescription **Oral** 0.610 (0.574-0.648) **Insulin** 0.746 (0.654-0.851) **Both** 0.489 (0.446-0.536)	 <0.0001 <0.0001 <0.0001

Checking models

The effect of increasing the number of integration points from 7 points to 50 points in the univariate analyses and the full fitted multivariate analysis did not make a difference to the odds ratio achieved for testing between December and March, previous HbA_{1c} or the fully fitted multivariate analysis (up to 4 decimal places) for a 3-level model of previous HbA_{1c} on either testing intervals that were less than 60 days or more than 366 days.

Testing logistic regression model fit

The fit of the three-level model (including both GP surgery and patient as random variables) was compared with a two-level model (with patient as the only random variable) using AIC and BIC. Both of these criteria were smaller in the 3-level model than in the two-level model suggesting that the three-level model was a better fit for the data (Table 2.16).

The residual interclass correlation indicated that, for re-testing HbA_{1c} within 60 days, approximately 6% of the variance was attributable to difference between GP practices and 18% was due to variance at the patient level. Residual interclass correlation for re-testing more than a year indicated that around 15% of the variability was explained by the GP practice and 36% at patient level (Table 2.16).

These results suggest that testing outside recommendations does vary at a GP practice level, and therefore inclusion of GP practice as a random variable in the model was appropriate.

Table 2.16 - Testing models using Akaike information criterion, Baysian information criterion and interclass correlation.

	Difference in AIC	Difference in BIC
<60 days – 2-level model	0	0
<60 days – 3-level model	-4680	-4668
>366 days – 2-level model	0	0
>366 days – 3-level model	-14,722	-14,711
	ICC	**95% CI**
<60 days – practice level	0.057	0.050-0.064
<60 days – patient level	0.181	0.174-0.188
>366 days – practice level	0.148	0.134-0.164
>366 days – patient level	0.364	0.352-0.376

2.3.4 Conclusions

Key findings

This work describes HbA_{1c} testing frequency across the UK and how testing outside of guidelines varies according to patient- and GP-level factors. It has been established that re-testing HbA_{1c} within 60 days of the previous test and re-testing more than a year from the previous test are both more common in the four months immediately prior to the QOF deadline on 31st March compared with other times of year.

Across the UK around 17% of all repeat HbA_{1c} tests were carried out at time intervals outside those recommended by guidelines. Over 8% of HbA_{1c} tests were carried out within 60 days of the previous test, 37% of which were in people with well-controlled diabetes. Similarly, over 9% of all repeat HbA_{1c} tests were more than a year from the previous test and 32% of these were in people with uncontrolled diabetes. Having a previous HbA_{1c} above 7.5% (58 mmol/mol) was strongly associated with increased odds of re-testing HbA_{1c} within 60 days and lower odds of re-testing more than a year from the previous test, compared with lower HbA_{1c}. These results were robust for those with type 1 and type 2 diabetes, and in a sensitivity analysis using a random test from each patient in the cohort.

Results from this analysis suggest that the number of patients who are receiving more than 8 tests over a 2-year period are decreasing over time. Despite this, the proportion of tests taking place outside guidelines has remained fairly constant over the 10-year period. This suggests that, overall, HbA_{1c} testing outside guidelines is distributed across many individuals, rather than some patients routinely receiving too many, or too few, tests.

Tests of the fit of the 3-level model suggest that HbA_{1c} testing outside guidelines varies between GP practice, with these differences accounting for up to 15% of the variance observed. These differences could be linked to geographic location of the practice, socio-demographic characteristics of the patient population or testing behaviour of individual GPs. There was evidence that there were differences in testing patterns in different parts of the UK, with Scotland and Northern Ireland being most likely to re-test HbA_{1c} very frequently, whereas London, the Midlands, the East, and the South West of England were least likely to re-test within 60 days. Conversely, those in London were much more likely to have more than a year between HbA_{1c} tests compared with any other part of the UK, and those in Scotland the least likely. More crucially, the significant association with more testing outside of guidelines at times of year prior to QOF deadline, suggests that at least some of this testing is GP- rather than patient-driven. Patient-level factors were associated with 36% of the variance which could be attributed to socio-demographic factors, comorbidities or patient behaviour.

The reasons for the variations in HbA_{1c} testing across the UK are not all clear, and may result from a combination of factors ranging from population demographics, deprivation, access to services, and local resources. Scotland had much lower odds of re-testing more than a year from the previous test compared with anywhere else in the UK, suggesting that GPs there may be proactively inviting patients to their diabetes reviews. There are several

initiatives which have been taken by the Scottish government to improve care of those with diabetes which may have had an impact on this (19, 20).

Strengths and limitations

To our knowledge this is the largest analysis to examine factors affecting HbA_{1c} testing frequency in a national cohort in the UK. The study population should be representative of the general population across the UK; however, because there may be regional differences in testing patterns, the results may not be representative of a defined population. This analysis was hypothesis driven which gives more weight to the findings. Including patients with type 1 and type 2 diabetes allowed comparison between testing patterns in these groups to explore whether there were differences. What was not tested in this dataset is whether the patterns found in this data were different prior to the introduction of QOF in 2004.

Using a mixed effects hierarchical model has made it possible to include multiple HbA_{1c} measures in each patient. Each patient had a minimum of three HbA_{1c} tests in this analysis, which may have favoured short testing intervals over long testing intervals and biased the results. However, a sensitivity analysis using a randomly selected test interval from each patient found similar results, suggesting that these findings are robust. An attempt has been made to consider factors which may have influenced patient or clinician HbA_{1c} testing behaviour as covariates in the analysis. However, other indications, such as deprivation, ethnicity or Charlson Comorbidity Index, which have not been analysed, could have influenced testing behaviour. Lipid-lowering or antihypertensive medication use was included in the analysis as a proxy for existing comorbidities, but many patients may have been taking these medications to reduce risk of future events; instead the Charlson Comorbidity Index could have been used as an indicator of comorbidities.

As there were a large number of covariates included in the multivariate analysis, it is likely that some of the positive associations found in this analysis were false positives. The main associations, however, association of frequency of HbA_{1c} testing with QOF dates and previous HbA_{1c}, had also been found in the John Radcliffe Hospital laboratory data, and were pre-specified in the CPRD analysis, giving additional confidence in this result. The nature of this retrospective analysis means that only an association between variables can be construed, rather than causation. Other patient-level factors, such as deprivation (measured as index of multiple deprivation) or ethnicity, both of which are associated with diabetes (21-23), were not included in the analysis but may have also been associated with testing outside of guidelines.

Although people with some life-threatening conditions were excluded from this analysis, it is acknowledged that there will be some people who remained in the analysis who had other conditions which make regular monitoring of glycaemic control or tight glycaemic control inappropriate or unfeasible; this is a limitation of this work. Moreover, some people included in the analysis may have been exempt from QOF due to age, frailty or existing comorbidities. This is reflected in the finding that those over 80 years of age were more likely to have more than a year between tests than younger people.

There are some inherent limitations in using this data. Some patients in this analysis may be people who have received monitoring in more than one location throughout the 10 year follow-up, which may be a factor contributing to some of the longer times between tests. It is also possible that that a number of apparently independent patient records may in fact be non-independent if people leave one practice and join another; however, the number of

patients affected is anticipated to be very small. Some of the HbA_{1c} requests included in this analysis may have been made from secondary care rather than from primary care.

For the purposes of this analysis people with missing data on smoking status were categorised as non-smokers. Although this was informed by previous research (18), it is unlikely to be completely accurate and may have influenced the results. It is possible that some of those categorised as having incident diabetes may have had an existing diagnosis which may have influenced the findings.

Discussion in the context of the literature

Although an analysis comparing how testing varies at different times of year has not previously been published, there have been reports of how QOF has affected performance in GP practices (24). In particular, practices which had been poor performers were found to make significant improvements in their performance across many quality indicators after the introduction of QOF in 2004. This analysis of CPRD data has found that HbA_{1c} testing outside guidelines is more frequent in the four months before the QOF deadline, suggesting that QOF may influence GP HbA_{1c} testing behaviour. Whether QOF may also be associated with timings of other tests in diabetes, for example blood pressure or albumin-creatinine ratio (ACR), or impacts testing behaviour in other conditions has not been addressed in this analysis.

Previous studies have reported on the frequency of HbA_{1c} testing in UK primary care settings (9, 11, 25), with outcomes ranging from the numbers of inappropriate test requests (9) to the implications of testing frequency on change in HbA_{1c} (11, 25). Our analysis is the largest cohort study to look at and report HbA_{1c} testing frequency in terms of patient demographics, effects of testing interval on the change in HbA_{1c}, trends over time, regional differences in testing across the UK and differences in testing patterns over the

year. No other study has compared differences in HbA_{1c} testing frequency across different parts of the UK. A recent study from the US reported that HbA_{1c} is over-tested in more than 60% of people with well-controlled diabetes (12). Our analysis has not found over-testing of HbA_{1c} on this scale in the UK.

Clinical implications

The results suggest that diabetes monitoring by clinicians is influenced by incentives. Re-testing HbA_{1c} within very short time intervals (within 60 days) may be appropriate for patients who had recently been prescribed a new medication to monitor response or adherence in these patients (14). Data from this analysis have shown that the majority of HbA_{1c} tests carried out within 60 days were in patients whose HbA_{1c} was very high. So although this degree of testing is not condoned in the guidelines, evidence suggests that some primary care clinicians may believe that re-testing HbA_{1c} within a short time interval is appropriate in some of their patients. In the *post-hoc* analysis, those over 80 years of age were found to be more likely to be tested outside guideline-recommended intervals than those under 80 years of age, suggesting that this population may have different requirements to younger patients. Patients with incident diabetes were more likely to be tested within recommended intervals compared with those with existing diabetes, which may be because GPs are more adherent to guidelines, or because these patients are more likely to attend appointments. Despite this, there were still over 27,000 repeat tests carried out within 60 days in those whose previous HbA_{1c} was below 7.5% which may be an overuse of resources. Crucially, there is no apparent clinical reason why intervals between repeat tests should vary over the course of the year.

Results from this analysis have found that those who have received a recent change in their medication are much less likely to receive a repeat test within 60 days, and are more likely to have longer than a year between tests than those without a medication change. It

is not clear why this may be the case, but it is possible that this is because the appointment for a medication change may take place weeks after the HbA_{1c} test. By the time the prescription has been collected, it could be 3-4 weeks before the patient starts taking the new medication. If HbA_{1c} was re-tested within 60 days of the previous test, the patient may only have been taking their medication for 2-3 weeks, and the test may therefore be unlikely to pick up any changes in HbA_{1c} following the previous test. Receiving a medication change *prior* to the previous HbA_{1c} test was, however, associated with increased odds of receiving a repeat test within 60 days, and decreased odds of receiving a repeat test more than a year from their previous test. This suggests that those who have received a recent medication change may in fact be more likely to be more closely monitored than those that have not.

The increase in HbA_{1c} testing outside of guidelines immediately prior to the QOF deadline suggests that GPs may be incentivised to monitor some patients more closely to improve their targets. It is not clear whether the patients who are more closely monitored in December to March were those who would benefit most from closer monitoring and treatment changes, were 'easy targets' who were already close to the QOF threshold, or were those who were adherent to appointments and medication. It is possible that pressures on GP workloads mean that use of incentive schemes is the only way to ensure that appropriate monitoring takes place in certain health conditions. These findings suggest that there may be an overuse of HbA_{1c} testing at certain times of year. Some patients who have not been tested for some time may be exposed to sub-optimal glycaemic control which may have long-term health implications with associated healthcare costs.

QOF guidance changed in 2013/2014 to reward testing taking place every 12 months rather than every 15 months. The majority of this cohort follow-up was during the previous 15-month guidance, which may have influenced the number of tests which were

performed at long time intervals. The changes in QOF guidance may have potentially affected clinician behaviour to result in a decrease in the numbers of tests taking place more than a year from the previous test.

The long-term health implications for those patients who receive HbA_{1c} testing outside of guidelines may be greatest for those with uncontrolled diabetes who are not receiving annual HbA_{1c} tests. The reasons behind these tests not taking place within guidelines cannot be established in this analysis, though some of these patients may be people who travel between different locations and may be receiving HbA_{1c} tests at another GP practice, or may be a result of other patient-related behaviours such as non-adherence to scheduled appointments. Exposure to high levels of glycaemia over extended periods of time increases the risk of diabetes-related complications which may then result in more consultations for other health-related problems (26).

2.4 Comparison of CPRD results with JR hospital results

The main findings from the Oxfordshire dataset have also been observed in the larger CPRD national dataset. This work has identified that more repeat testing outside guidelines takes place in the 4 months prior to the QOF deadline, which is a key finding. Additionally those with a previous HbA_{1c} above 7.5% receive more tests within 60 days suggesting that those with uncontrolled diabetes are being more closely monitored. Both datasets also found that there were similar proportion of tests carried out outside guidelines, and fewer HbA_{1c} tests are carried out in April, August and December than at other times of year.

2.5 Discussion and clinical implications

This work suggests that clinician behaviour may be influenced by incentives, manifested in increased rates of testing outside recommendations, to attempt to meet GP targets. Guidelines recommend monitoring HbA_{1c} two to four times a year (2) which, if implemented, could minimise deteriorations in HbA_{1c}. Around one in six HbA_{1c} tests takes place outside of guideline recommendations; ways to encourage regular and appropriate monitoring, particularly in those with poorly-controlled diabetes, now need to be identified. This may be through incentive schemes to encourage HbA_{1c} testing appropriate to the individual, or through the introduction of different types of testing which may be more convenient to patients who require closer monitoring. Potentially the use of point-of-care HbA_{1c} testing could allow opportunistic testing in some patients, particularly those who are not regular attenders. This would allow an HbA_{1c} test and adjustment to medication to take place in a single consultation. It could therefore reduce the numbers of tests which are carried out at inappropriately long time intervals. In the following chapters I will explore how point-of-care HbA_{1c} testing could be used in diabetes monitoring in primary care. The work covered in this chapter describing HbA_{1c} testing patterns in primary care will help to inform how point-of-care HbA_{1c} testing may be used both for meeting quality deadlines, or for those patients who may need more frequent or opportunistic testing. The next three chapters will summarise the accuracy of point-of-care devices, explore how point-of-care testing could be implemented into clinical practice, and gather patient and clinician views and potential mechanisms for behaviour change.

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Chapter 3 : Accuracy of point-of-care HbA_{1c} devices

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3.1 Introduction

This chapter will provide an overview of the point-of-care (POC) HbA_{1c} test devices which are commercially available, and systematically review the literature on the performance of these devices. First the characteristics of the POC devices will be summarised, tabulated and compared. This will then be followed-up with a systematic review and meta-analysis of evaluation studies published in the peer reviewed literature, which compare performance of POC devices with laboratory reference methods. Data from published laboratory and field evaluations will be combined to enable comparison of performance across devices. This approach, to combine data on HbA_{1c} devices, has not previously been used and will contribute to the literature around these technologies. This will help clinicians and patients to make more informed decisions. For the purposes of my DPhil project, the information I have gathered and synthesised in this chapter will be used to select a device to purchase for the data collection element of my research detailed in Chapter 4.

3.1.1 Background and rationale

As highlighted in Chapter 1, one of the potential barriers to the adoption of POC HbA_{1c} testing raised by both patients and healthcare professionals is concern about whether the tests are sufficiently accurate for use in clinical practice (1). Concerns about device accuracy could potentially influence the adoption of POC testing by GP practices in the United Kingdom. Numerous evaluations have been published on POC HbA_{1c} devices, but there have been few attempts to synthesise the literature in a systematic manner to enable comparison between devices. A single review, published in 2014, has combined data on correlation coefficients from five studies of three point-of-care devices (2). Most of the evaluations which have been published on POC HbA_{1c} devices have been undertaken by laboratory professionals, meaning that it remains unclear whether the performance of these

devices is any different if the operator is a nurse or doctor. Moreover, these devices are intended for use in a point of care setting, which may be less likely to have environmental control, and may have greater temperature fluctuations compared with a laboratory setting. It is not well understood whether setting or type of operator could affect device performance or result. Having this information may assist end users of POC tests in making informed decisions about the suitability of a particular device for their purposes. It would also make end-users aware of the levels of uncertainty likely to be encountered in the result.

3.1.2 Objectives

1. To summarise the characteristics of POC HbA_{1c} test devices.
2. To assess the accuracy of commercially available POC HbA_{1c} test devices by systematically reviewing the literature and conducting a meta-analysis of device accuracy.
3. To use the above information to select the most appropriate device to use in a data collection study.

3.2 Introduction to point-of-care HbA_{1c} test devices

This section provides a summary of the point-of-care technologies and characteristics of the devices which are commercially available and capable of measuring HbA_{1c} from a finger-prick capillary blood sample.

3.2.1 Technologies

The majority of laboratory methods for the detection of HbA_{1c} use one of three methods: cation-exchange chromatography, which is based on differences in charge; affinity chromatography, which is based on structural differences; or immunoassay methods, which are based on chemical reactivity (3). Cation exchange methods are currently only

used in laboratory-based instruments, whereas all the available POC devices use either affinity chromatography or immunoassay methods to measure HbA_{1c}. These are briefly described below.

In cation-exchange chromatography the non-glycated and glycated parts of the haemoglobin are separated in a charged column by their overall charge. HbA_{1c} passes through the column faster than HbA which forms the major part of adult haemoglobin (3). Because of their separation in the column, they elute at different times, and are then measured chromatographically. The relative peak heights are used to calculate the percent HbA_{1c}. The advantage of this method over the other methods is higher precision; however they are known to be subject to interference by some haemoglobin variants (4).

In affinity separation, the glycated portion of haemoglobin reversibly interacts with boronic acid which is immobilised to the surface of a chromatography column, and is thus retained in the column. The non-glycated haemoglobin passes directly through the column, where it is measured chromatographically; the glycated haemoglobin is then released by reagents to displace it from the boronate, and is also measured chromatographically (4, 5).

Immunoassay methods use antibodies which bind to N-terminal peptides on the haemoglobin molecule and are measured using turbidometric methods (4, 6). A commonly used method is called latex agglutination, in which the antibodies are bound in latex particles (7). These work by adding an excess of antibody to the patient sample which binds up all the HbA_{1c}, the remaining antibody then agglutinates to form clumps which make the sample cloudy. This cloudiness, or turbidity, can be measured photometrically (4).

Unlike cation exchange chromatography, both affinity chromatography and immunoassay have the advantage that they are not affected by the most common haemoglobin variants. Affinity separation chromatography is the favoured method for measuring HbA_{1c} in those with haemoglobin variants (8). These methods are, however, prone to greater imprecision than seen with cation exchange high performance liquid chromatography (HPLC) methods (4, 9), and some methods are reported to not meet minimum acceptability criteria for precision and accuracy (10-12).

In addition to these methods, other technologies for measuring HbA_{1c} are capillary electrophoresis (13), which is no longer used in most laboratory settings (4), and emerging enzymatic methods, in which the direct measurement of HbA_{1c} is possible using enzymes and can be measured spectrophotometrically (14). These are now used in some laboratory instruments (15, 16).

3.2.2 HbA_{1c} Point-of-care device characteristics

According to a recent report there are currently 23 point-of-care devices in use internationally (12). The major features of 13 of these devices, for which performance evaluations have been published in the peer-reviewed literature, are summarised below and in Table 3.1. In brief: all devices are able to measure HbA_{1c} from a drop of capillary blood, though anti-coagulated venous blood can also be used. The required sample volume varies from 1 to 10µl, and the time to test result ranges from 3 to just under 8 minutes. The amount of sample preparation varies from device to device, with some requiring no more than application of the blood, whereas others require some additional steps prior to beginning the analysis. The devices vary in size from 63.5x10x51 mm^3 (A1cNow) to 290x270x340 mm^3 (B-analyst) and weights vary from 0.2 to 9.5kg. They typically have an HbA_{1c} range of around 4-14% (20-130 mmol/mol).

Table 3.1 - Summary of characteristics of POC HbA_{1c} devices.

Name	Manufacturer	Sample type	Volume	Preparation time	Analysis time	Cost	Size of device (mm^3)	Weight	Technology	Range	Barcode scanner
Afinion	Alere	Capillary or venous	1.5 µl	none	3 mins	£2500	320 (d) × 170 (h) × 170 (w)	5 kg	Boronate affinity	4-15% 20-140 mmol/mol	y
A1cNow (12)	PTS Diagnostics, US	Capillary or venous	5 µl	Shake sample for 5 seconds	5 mins	$129 for 10 tests	63.5 (d) × 10 (h) × 51 (w)	0.18kg	Immunoassay	4.0-13.0% 20.2-119 mmol/mol	n
A1c Gear (12)	Sakae Corporation, Japan	Capillary or venous	1 µl	-	6 mins	-	280 (d) × 290 (h) × 230 (w)	-	Immunoassay	4.0-13.0%	y
B-analyst	Menarini, Italy	Capillary or venous whole blood, plasma or serum	4 µl	none	7 min 40s	-	290 (d) × 270 (h) × 340(w)	9.5 kg	Latex agglutination immunoassay	3.3-12.6%	y
Cobas b101	Roche Diagnostics, Switzerland	Capillary or venous	2 µl	none	<6 mins	-	234 (d) × 184 (h) × 135 (w)	2 kg	latex agglutination immunoassay	4-14%	y
Clover A1c	Neon Diagnostics, UK	Capillary or venous	4µl	Shake reagent	5 mins	-	202 (d) × 89 (h) × 136 (w)	0.5 kg	Boronate affinity	4-14%	y
DCA Vantage	Siemens, Germany	Capillary or venous	1 µl	none	6 mins	£2460	277(d) × 254(h) × 287(w)	3.88 kg	Immunoassay	2.5-14%	y
HemoCue HbA1c 501	Hemocue AB, Sweden	Capillary or venous	4 µl	None	5 mins	£1088	217 (d) × 136 (h) × 198 (w)	1.6kg	Boronate affinity	4.0-14.0% 20-130 mmol/mol	y

InnovaStar	DiaSys, Germany	Capillary or venous whole blood, plasma	10 µl	Shake reagent	6.5 mins	-	170 (d) × 150 (h) × 200 (w)	4 kg	Turbidimetric Immunoassay	3-14%	y
Nycocard	Alere Inc., US	Capillary or venous	5 µl	manual precipitation, application, washing (~4mins)	3 mins	-	170 (d) × 70 (h) × 200 (w)	0.54kg	Boronate affinity	4.0-15.0% 20-140 mmol/mol	-
Quo-Test	EKF Diagnostics, UK	Capillary or venous	4 µl	none	4 mins	£1267	135(d) × 205 (h) × 205(w)	1.3 kg	Boronate affinity	4.0-15.0% 20-140 mmol/mol	y
Quo-Lab	EKF Diagnostics, UK	Capillary or venous	4 µl	none	4 mins	-	135(d) × 95 (h) × 205(w)	0.7 kg	Boronate affinity	4-15%	y
SD A1cCare	SD Biosensor, Korea	Capillary or venous	5 µl	Mix with buffer	3 mins	-	96 (d) × 56 (h) × 163 (w)	0.45 kg	Immunoassay	4-15%	y

3.2.3 Summary

The majority of the POC devices are marketed as being easy to use with minimal training required, and are suitable for use in a point of care setting. Some of the devices do, however, report that they should only be used within certain temperature limits, which may make them unsuitable for use in some settings if temperatures are likely to be high.

3.3 Systematic review of analytical performance of POC HbA_{1c} devices

3.3.1 Background

Few published evaluations have compared performance between POC HbA_{1c} devices, which makes it difficult for clinicians or patients to make a judgement on whether a particular device may suit their clinical needs. Of those evaluations which compared more than one device, the majority have taken place in a laboratory setting and analyses were carried out by laboratory professionals (10, 11), rather than at a point of care or clinical setting where these devices will ultimately be used (17, 18). It therefore remains unclear whether performance may differ between settings, or is dependent on whether the end-user is a laboratory professional or a clinician.

One way to answer the questions about comparison between devices and across settings is to use systematic review and meta-analysis. Meta-analysis has an advantage over individual studies to answer some research questions because it has greater power, particularly in cases where individual studies are too small. It also enables different research questions to be answered by comparing outcomes or effect sizes in different subgroups (19). Because meta-analysis usually uses aggregate data from published studies, it is limited by the quality of the included studies and the data that is reported. When the quality of published studies is good, systematic review combined with meta-analysis is generally considered as the most robust evidence on which to base clinical

decisions (20). Meta-analysis can be used to combine continuous or dichotomous data, or data on diagnostic accuracy. To compare performance of devices, data in included studies would have to be reported using the same measure. Some commonly used methods to compare laboratory measurements are discussed below.

Methods for comparison of measurements

Comparison between two continuous analytical measurements can be carried out in several ways. A commonly used method is to use linear least squares regression and report the correlation coefficient. This method, however, has several drawbacks, most notably because two methods can have a strong linear relationship, and thus a high correlation coefficient, even when the methods do not agree (21). Furthermore, comparisons using least squares regression assume that the reference measurement gives a definitive result, meaning the correctness of the reference method is non-questionable. Because this is not usually the case in laboratory measurements, other methods of comparison are more suitable in most situations. Some of the statistical methods which are more appropriate to use to compare analytical methods are Bland and Altman plots, Deming regression and Passing and Bablock regression (22).

Deming regression and Passing and Bablock regression differ from linear regression in assuming that measurement errors exist in both the analytical methods, and that these have the same distribution (22, 23). Deming regression assumes a normal distribution of errors. Estimation of the regression line by Deming method uses a ratio of the standard deviations between the two methods (24). The Passing-Bablock method does not make assumptions about the distribution of samples or measurement errors, is not sensitive towards outliers, and assumes imprecision in both methods (22). Both these methods measure the linearity of the relationship between two measurements rather than their agreement.

In Bland-Altman plots, the differences between the two measurements are plotted against the mean of the two measurements. This makes it possible to both visualise the difference between two measurements, and to calculate the mean difference (or bias) and standard deviation (SD) to summarise the agreement between the methods (21).

Another way that tests can be compared is to evaluate the ability of a test to accurately diagnose a disease (in this case diabetes). A diagnostic accuracy study compares the numbers of cases which would be detected or missed if the new test were to be used compared with a reference method (25).

In terms of clinical applicability and interpretation, data on diagnostic accuracy and mean bias from Bland-Altman plots provide the most informative information on a test performance. However, the equation for a regression line is able to provide information on how the test performs at different points across the analytical range. Therefore, using the regression equation, it is possible to establish whether a test is likely to give a higher or lower reading at a certain cut-point than the reference test, which is not possible using the other methods.

Here, a systematic review and meta-analysis will be used to compare measures of POC HbA_{1c} device performance with National Glycohemoglobin Standardization Program (NGSP) accepted laboratory methods.

3.3.2 Aims and Objectives

Aim

To assess the accuracy and precision of HbA_{1c} measured using POC testing technology.

Objectives

To combine data from studies measuring HbA_{1c} using POC devices to compare the following:

i. Bias and precision of POC device compared with laboratory method across entire therapeutic range.
ii. Sensitivity and specificity of POC device at diagnostic and treatment thresholds compared with laboratory methods.
iii. Bias of each POC instrument at various cut-points across a range of HbA_{1c} levels including diagnostic and treatment thresholds compared with laboratory methods.
iv. Performance of POC device when used by different operators (specifically health care professional versus laboratory professional).
v. Performance of POC device in different settings (specifically laboratory-based assessment compared with point of care setting).

3.3.3 Methods

Searches of MEDLINE (1950-2015), EMBASE (1980-2015) and Web of Science databases were first carried out on 2nd January 2014 using search terms for glycated haemoglobin and index point-of-care devices. The full Medline search strategy is provided in Appendix 2, Table A1. An update to the searches was carried out on the same three databases on 29th June 2015. Hand searches of original articles, reviews and conference abstracts were also carried out. Reports in all languages were considered for inclusion.

Titles and abstracts of retrieved references were screened by two reviewers; included papers were screened for full eligibility based on the following criteria:

Inclusion criteria:

- Any study in which both a POC HbA_{1c} test (defined as any instrument designed to use capillary blood which can provide a rapid quantitative measurement of HbA_{1c} at the point-of-care, thereby allowing immediate clinical decisions to be made) and a laboratory-based HbA_{1c} instrument are performed on each patient or sample.
- Reported outcomes included bias or regression line equation between the POC and laboratory test.
- Full text articles, conference abstracts or letters detailing unpublished study results were included as recommended by the Cochrane Collaboration (19).
- Published in a peer-reviewed journal.

Exclusion criteria:

- Studies in which the POC HbA_{1c} and the laboratory HbA_{1c} were carried out more than 1 week apart were excluded to minimise differences between measurements.
- Studies carried out on POC analysers which were not commercially available on 30 November 2015.
- Company literature reporting device performance which was not clearly carried out by a third party or subject to an external peer-review process.

The systematic review protocol was registered on the PROSPERO database (Registration number CRD42013006678).

Data extraction

Data were extracted by two reviewers on the following: type of sample used for the evaluation (capillary or venous blood, where reported), operator (clinical: doctors, nurses

or health-care assistants; laboratory professional or other), setting (clinical point of care, laboratory setting or other), number of participants, proportion with diabetes, the proportion of female participants, mean age, mean HbA_{1c} (in either SI units [mmol/mol] or NGSP units [%]), where reported. Data on outcome measures: mean (±SD) bias (defined as mean of the difference between POC and laboratory test [POC- laboratory] for each sample measured), regression equations for the relationship between POC and laboratory measurement and sensitivity/specificity data for diagnostic accuracy at thresholds of 6.5% (48 mmol/mol) and 7.5% (58 mmol/mol). These thresholds were selected because 6.5% is the diagnostic cut-off for diagnosis of diabetes and 7.5% is a common treatment threshold as recommended in NICE guidelines (26).

Instrument-specific data were also extracted: POC device make and model, make and model of laboratory tests used and reported laboratory accreditation or certification.

Study quality and risk of bias was graded according to the QUADAS 2 risk of bias table (27) as recommended by The Cochrane Collaboration (28). We also recorded whether the study was industry funded and whether the range in HbA_{1c} was sufficiently broad, defined as 5-11% HbA_{1c} (31-97 mmol/mol). All studies deemed to be at high risk of bias for at least one criterion were excluded in a sensitivity analysis.

For reports in which multiple laboratory tests were used, the cation exchange high performance liquid chromatography (HPLC) method was selected as the comparator method for the analysis, as this is reported to be most accurate and precise (29-31), compared with affinity chromatography or immunoassay. If duplicate POC tests were performed using different reagent lot numbers, then both comparisons were included in the meta-analysis.

In general, studies did not report sensitivity or specificity for diagnosis of diabetes. However, this was sought from authors and, in cases where it was not provided, it was estimated from correlation plots or Bland-Altman plots by counting the numbers of visible dots in each quadrant. In this manner, sensitivity and specificity data were obtained at HbA_{1c} thresholds of 6.5% (48 mmol/mol) and 7.5% (58 mmol/mol). Where there were sufficient data available for one device, these were combined using diagnostic accuracy meta-analysis (32).

Studies which reported the equation for the regression line based on the comparison of the POC device and laboratory test were also combined in a separate analysis. The regression equation was used to calculate the POC HbA_{1c} at three points over the therapeutic range for laboratory HbA_{1c} values of 6.5% (48 mmol/mol), 7.5% (58 mmol/mol), and 10% (86 mmol/mol), for each study. These cut-points were selected as diagnostic threshold (6.5%), treatment threshold (7.5%), and a high HbA_{1c} value (10%) for purposes of comparing levels of bias. The results at each cut-point were combined by taking the mean value of all studies separately for each device. If equations from two different regression methods were reported, then results from Deming or Passing-Bablock regression methods were selected in preference to linear regression, as these take account of errors in both the x- and y-directions and are therefore more suitable for comparison of methods (23).

Precision data, recorded as coefficient of variation (CV), calculated by dividing the SD by the mean, were extracted for HbA_{1c} measured in NGSP (%) units for all included studies in which this was reported. Data were combined by taking the average for each device for both within-run and between-run precision at low (<6%), medium (6-8%), and high (≥8%) levels of HbA_{1c}, as well as combining all the data to give total CV regardless of whether the samples were control samples or patient samples.

Statistical analysis

All analyses were carried out using Stata 12.1SE (StataCorp, TX). Data on mean bias between POC assay and laboratory test (POC HbA_{1c} − laboratory HbA_{1c}) and standard deviations (SD) were combined using random effects Dersimonian and Laird meta-analysis. A random effects model was chosen to combine data because of unexplained heterogeneity between studies, and the wider confidence interval from a random effects model better reflects the uncertainty in the mean value (19). Data for each POC instrument were separately pooled. Forest plots were generated to show the following:

1) Mean bias in each study along with 2SD error bars to show the scatter in the data contributing to each individual study. Results were kept in subgroups for each device but data were not pooled;

2) Mean bias and 95% confidence intervals (CI) for each study, and pooled estimates with prediction intervals, stratified into subgroups of POC device to compare levels of bias between studies and between devices. Inclusion of prediction intervals in the plot shows the approximate predictive distribution boundaries in which a future study may fall;

3) Standard deviations of the mean bias in each study, and standard error of the SD (estimated using methods reported by Ahn and Fessler, 2003 (33)). Pooled estimates of the SD and prediction intervals were shown for each POC device to enable comparison of the levels of uncertainty in the data between studies for each device.

The following estimates were made: median bias was approximated to mean bias; if standard deviation or standard error were not reported, then these were imputed by taking the mean standard deviation from other studies of the same device as recommended in the Cochrane Handbook (19). Studies in which estimates were made for data extraction purposes, and those in which there were aspects of the methodology that could contribute

to bias in the reported findings, were excluded in sensitivity analyses. A sensitivity analysis was also carried out to examine the effect of only including reports which specified that the laboratory HbA_{1c} was measured in a NGSP accredited laboratory. Because of potential changes in calibration over time, an analysis was conducted to restrict the data only to those studies published in 2014-2015 in order to report the most up-to-date calibration. Subgroup analyses and meta-regression were conducted to explore how bias and SD changed over time, and in studies published in the most recent 10 years compared to earlier times. Subgroup analyses were carried out, where possible, to explore whether there were any differences between operator (clinical or laboratory) and setting (point of care or laboratory), adult or child patients or blood sample type (venous or capillary) within a single device. Meta-regression was carried out where there were sufficient studies to establish whether using the device in different settings (point of care or laboratory) were significantly different from one another. *Post-hoc* subgroup analyses and meta-regression were carried out to explore the impact of industry funding on effect sizes in three devices, Afinion, A1cNow and DCA.

Data on diagnostic accuracy were combined using the *metandi* command in Stata (34). This displays the combined sensitivity and specificity from the studies and generates a hierarchical summary receiver operator curve in which an overall estimate of diagnostic accuracy is generated to graphically display the linked nature of the sensitivity and specificity (32).

3.3.4 Results

Searches and study characteristics

The first search carried out in the three databases identified 1483 records, and the update search identified a further 256 records, to give a total of 1739 records retrieved from

searches and a further six records were identified from reference lists of other articles. There were 435 duplicate records which were excluded, leaving 1310 articles for title and abstract review. Articles were rejected for the following reasons: studies were not carried out in humans (n=20), the study did not report data on bias or regression equation (n=823), point-of-care devices were not used (n=135), HbA_{1c} was not measured (n=78) or technologies were clearly not commercially available (n=7), totalling 1063 excluded records. The remaining 247 articles were screened for full eligibility and a further 172 were excluded for the following reasons: an POC HbA_{1c} test was not used (n=15), it was not an evaluation study (n=50), it was a duplicate article (n=8), there was no laboratory test (n=17), did not report numerical data on device accuracy, the device was not commercially available, the article was not peer reviewed (n=20) or data could not be combined in a meta-analysis (for example percent bias or only reporting a correlation coefficient from a regression equation) (n=62). A further 6 studies were excluded because they were carried out in people with haemoglobin variants (35, 36) or because data could not be extracted (37-40). A total of 69 studies were included in the systematic review reporting accuracy data from 13 devices which were commercially available in November 2015. Fifty-nine studies were included in the meta-analysis of mean bias between POC and laboratory HbA_{1c} and ten studies reported the regression equation only. The flow chart of included articles is shown in Figure 3.1.

Fifty-two included papers were full text articles, fifteen were conference abstracts, and two were letters or comments. Seven studies were conducted exclusively in children (41-47). Some studies reported results from multiple devices, or multiple lot numbers from the same device, leading to 105 comparisons in the meta-analysis. Nine of the comparisons did not report which instrument was used for the laboratory comparator analyser; of the

remainder, eighty-eight used ion exchange method, four used affinity chromatography and four used immunoassay. Characteristics of all the included studies are shown in Table 3.2.

Devices compared in the meta-analysis of mean bias were A1cgear (n = 1), A1cNow (n = 17), Afinion (n = 12), B-analyst (n = 5), Clover (n = 2), Cobas b101 (n = 5), DCA 2000/Vantage (n = 39), HemoCue (n = 2), InnovaStar (n = 5), Nycocard (n = 6), Quo-Lab (n = 3), Quo-Test (n = 7), and SDA1cCare (n = 1). The majority of studies reported bias in HbA_{1c} in % units with only two studies reporting in SI units, mmol/mol (48, 49).

Figure 3.1- Flow chart

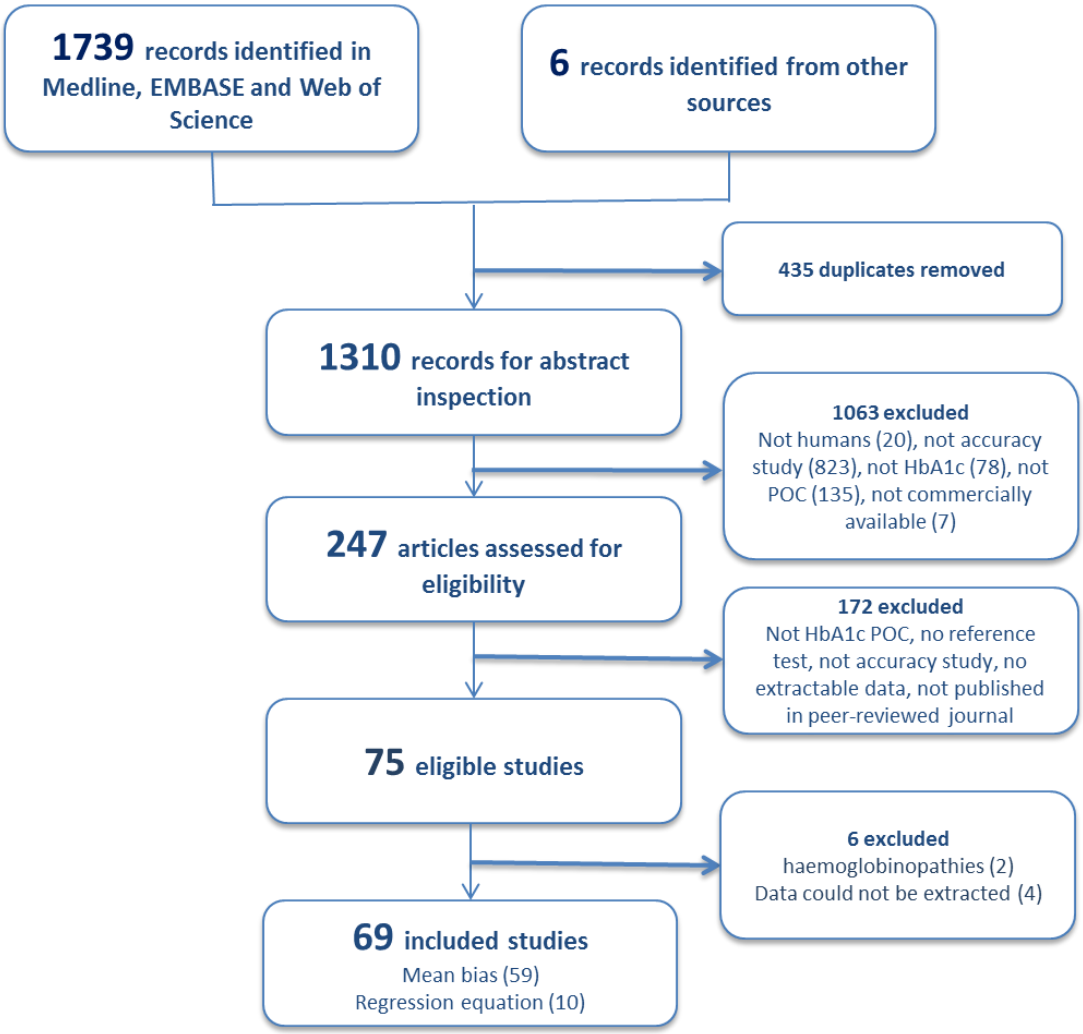


Table 3.2 - Table of included studies.

Author	Year	POC device(s)	Comparator method	POC sample	Operator	Setting	Number of patients	Mean HbA_{1c} (%)	Reporting
Affret (50)	2015	A1cNow	Vitros 5.1 FS immunoassay	capillary	ns	POC	55	7.3	Mean bias, precision
Arabadjief (51)	2009	Afinion	Biorad Variant II ion exchange	ns	ns	ns	110	ns	Regression equation
Arsie (52)	2000	DCA 2000	Diamat ion exchange	venous	laboratory	laboratory	117	7.2	Mean bias, regression equation, precision
Azevedo (53)	2011	DCA 2000 Quo-Test	ns- HPLC	capillary	ns	ns	52	8.1	Mean bias
Berry (48)	2014	Cobas b101, HemoCue, DCA Vantage, Afinion	Biorad D10 ion exchange	ns	ns	ns	17-49	ns	Mean bias
Boz (54)	1997	DCA 2000	ns- HPLC	capillary	ns	POC	100	7.9	Mean bias, regression equation
Calgliero (17)	1999	DCA 2000	ns- HPLC	capillary	clinical	POC	264	8.6	Mean bias, regression equation
Carrera Font (55)	2011	Afinion	Menarini HA 8106 ion exchange	capillary	clinical	POC	94	7.3	Regression equation, precision
Chan (41)	2014	DCA Vantage	Biorad Variant II ion exchange	ns	ns	ns	72	5.7	Mean bias, regression equation
Chang (56)	2010	A1cNow	Tosoh 2.2 ion exchange	capillary	clinical/ patient	POC	99 178	ns	Regression equation
Clark (57)	2005	A1cNow	Tosoh 2.2 ion exchange	capillary & venous	laboratory	laboratory	499	ns	Mean bias, regression equation
Criel (58)	2015	Cobas b101, Afinion, B-analyst	Menarini HA 8106 ion exchange	ns	ns	ns	40	ns	Mean bias
Dupuy (47)	2013	DCA Vantage	Menarini HA 8106 ion exchange	venous	ns	ns	124	ns	Mean bias, regression equation, precision
Dupuy (59)	2014	Afinion	Menarini HA 8160 ion exchange	venous	laboratory	laboratory	155	ns	Mean bias, regression equation, precision

Author	Year	POC device(s)	Comparator method	POC sample used	Operator	Setting	Number of patients	Mean HbA_{1c} (%)	Reporting
Ejilemele (60)	2015	A1cgear	Biorad Variant II ion exchange	venous	laboratory	laboratory	120	8.1	Mean bias, regression equation, precision
El Arabi (42)	2013	DCA Vantage	Menarini HA 8160 ion exchange	capillary	clinical	POC	120	ns	Mean bias, precision
Estevez (61)	2014	DCA Vantage	Menarini HA 8160 ion exchange	venous	ns	ns	42	ns	Mean bias, regression equation
Ginde (62)	2008	A1cNow	ns - HPLC	capillary	laboratory	POC	161	5.8	Mean bias
Gounden (63)	2012	DCA	Siemens Adiva 1800 immunoassay	venous	laboratory	laboratory	20	ns	Regression equation, precision
Greaves (43)	2005	DCA 2000	Bio-Rad D10 ion exchange	capillary & venous	ns	POC & laboratory	228	ns	Mean bias, regression equation, precision
Guerci (64)	1997	DCA 2000	Diamat ion exchange	capillary	ns	POC	1016	ns	Mean bias, regression equation
Harris (65)	2000	DCA 2000	ns - HPLC	capillary	clinical	POC	102	ns	Mean bias
Hawkins (66)	2003	DCA 2000	Diastat ion exchange	venous	laboratory	laboratory	110	6.8	Mean bias, regression equation, precision
Heng (36)	2015	Cobas b101	Roche Tina-quant A1c.gen3 immunoassay	capillary	ns	ns	47	ns	Mean bias, regression equation
Holmes (67)	2008	DCA 2000	Biorad Variant II ion exchange	venous	laboratory	laboratory	24, 45, 21	ns	Mean bias, regression equation
Jiang (68)	2014	A1cNow	Biorad Variant II ion exchange	capillary	clinical	POC	1618	7.0	Mean bias, regression equation
Jou (69)	2013	A1cNow	Tosoh G8 ion exchange	venous	ns	ns	57	ns	Mean bias, regression equation
Karami (70)	2014	Nycocard	Knauer affinity	venous	laboratory	laboratory	58	5.8	Mean bias, regression equation
Knaebel (71)	2013	A1cNow	Tosoh G8 ion exchange	venous	ns	ns	40	ns	Mean bias, regression equation, precision
Leal (72)	2009	A1cNow	ns	capillary	pharmacist	POC	47	8.1	Mean bias

Author	Year	POC device(s)	Comparator method	POC sample used	Operator	Setting	Number of patients	Mean HbA_{1c} (%)	Reporting
Leca (73)	2012	DCA Vantage	Tosoh G8 ion exchange	venous	clinical	POC	100	7.3	Mean bias, regression equation
Lee (74)	2010	Afinion	Bio-Rad D10 ion exchange	venous	ns	ns	40	ns	Regression equation, precision
Lee (75)	2015	SDA1c Care	Biorad Variant II ion exchange	venous	laboratory	laboratory	150	ns	Mean bias, regression equation, precision
Lenters-Westra (76)	2009	DCA Vantage	Tosoh G7 ion exchange	venous	laboratory	laboratory	40	ns	Regression equation
Lenters-Westra (10)	2010a	DCA Vantage Afinion InnovaStar Clover Nycocard	Tosoh G7 ion exchange	venous	laboratory	laboratory	40	ns	Mean bias, regression equation, precision
Lenters-Westra (77)	2010b	Quo-Test	Tosoh G8 ion exchange	venous	laboratory	laboratory	40	ns	Mean bias, regression equation, precision
Lenters-Westra (11)	2014	DCA Vantage Afinion InnovaStar Quo-Test Quo-Lab B-Analyst Cobas b101	Tosoh G8 ion exchange	venous	laboratory	laboratory	40	ns	Mean bias, regression equation, precision
Malkani (78)	2013	DCA Vantage	Tosoh G8 ion exchange	ns	clinical	POC	45	ns	Mean bias, regression equation
Manley (79)	2014	DCA 2000 A1cNow	Primus Ultra 2 affinity	venous	laboratory	laboratory	128	ns	Mean bias
Marley (80)	2015	DCA 2000	Cobas Integra 800 immunoassay	capillary	clinical	clinical	241	ns	Mean bias
Martin (81)	2005	DCA 2000	Biorad Variant II ion exchange	capillary	ns	POC	88	7.1	Mean bias
Mattewal (82)	2007	A1cNow	Tosoh 2.2 ion exchange	venous	laboratory	laboratory	34	7.1	Mean bias, regression equation, precision
Menendez-Valladares (83)	2015	B-analyst	Menarini HA8140 ion exchange	venous	laboratory	laboratory	120	-	Mean bias, regression equation

Author	Year	POC device(s)	Comparator method	POC sample used	Operator	Setting	Number of patients	Mean HbA_{1c} (%)	Reporting
Nam (84)	2011	A1cNow	ns	capillary	laboratory	POC	83	9.1	Mean bias, regression equation
Peterson (85)	2010	DCA Vantage Afinion	Biorad Variant II ion exchange	ion exchange	laboratory	laboratory	86/88	7.9	Mean bias, precision
Phillips (49)	2014	Quo-Test, HemoCue, Afinion, B-analyst	Menarini ion exchange	venous	ns	ns	39-80	ns	Mean bias
Pope (44)	1993	DCA 2000	Diamat ion exchange	capillary	clinical	POC	15-24	ns	Mean bias, precision
Rossi (86)	2015	A1cNow	Tosoh ion exchange	capillary	laboratory	laboratory	81	ns	Mean bias
Sanchez-Mora (87)	2011	DCA Vantage Afinion	Menarini HA 8106 ion exchange	venous	laboratory	laboratory	53	ns	Mean bias, precision
Schweitzer (88)	2012	A1cNow	Biorad Variant II ion exchange	ns	ns	ns	453	8.6	Mean bias
Shemesh (89)	2003	DCA 2000	Pharmacia MonoS ion exchange	venous	ns	POC	39	6.5	Mean bias
Shemesh (90)	2006	DCA 2000	Pharmacia MonoS ion exchange	venous	ns	POC	117	5.5	Mean bias
Shephard (91)	2006	DCA 2000	Pharmacia MonoS ion exchange	capillary	ns	ns	100	7.1	Mean bias, precision
Shimoda (92)	2013	A1cNow	Tosoh G7 ion exchange	venous	clinical	POC	144	7.3	Mean bias, regression equation
St John (18)	2006	DCA 2000 A1cNow Nycocard	Primus CLC330 affinity	venous	clinical	POC	112	ns	Mean bias, regression equation, precision
Strojek (93)	2014	A1cNow	ns - HPLC	ns	ns	ns	219	ns	Regression equation
Szijarto (94)	2014	DCA Vantage	Biorad Variant II ion exchange	venous	laboratory	laboratory	102	ns	Regression equation
Szymezak (95)	2008	DCA Vantage	Biorad Variant II ion exchange	venous	laboratory	laboratory	100	ns	Mean bias, precision

Author	Year	POC device(s)	Comparator method	POC sample used	Operator	Setting	Number of patients	Mean HbA_{1c} (%)	Reporting
Tamborlane (45)	2005	DCA 2000	Tosoh A1c 2.2 Plus ion exchange	capillary	-	POC	ns	ns	Mean bias
Thueringer (96)	2012	A1cNow	Biorad Variant II ion exchange	capillary	patients	POC	50	9.9	Mean bias
Twomey (97)	2008	DCA 2000	Biorad Variant II ion exchange	venous	laboratory	laboratory	ns	ns	Mean bias, precision
Villar-del-Campo (98)	2014	DCA	Menarini ion exchange	capillary	clinical	clinical	102	6.5	Mean bias
Wan Mohd Zin (99)	2013	Afinion Quo-Test	Adams HA8160 ion exchange	venous	ns	ns	139	7.1	Mean bias, regression equation
Wehmeier (100)	2012	InnovaStar	ns	venous	laboratory	laboratory	30	ns	Mean bias
Williams (101)	2014	Quo-Lab	Biorad Variant II ion exchange	venous	ns	ns	41	ns	Mean bias
Wiwanitkit (102)	2012	DCA	Cobas immunoassay	ns	ns	ns	40	ns	Regression equation
Wood (46)	2012	DCA Vantage Afinion	Tosoh ion exchange	capillary	clinical	POC	40	ns	Mean bias, precision
Woodworth (103)	2014	DCA Vantage	Biorad Variant II ion exchange	venous	ns	ns	40	ns	Regression equation, precision
Zhou (104)	2014	DCA	Tosoh G8 ion exchange	venous	ns	ns	50	ns	Mean bias, regression equation, precision

ns – not specified

HPLC – high performance liquid chromatography based method: ion exchange – ion exchange chromatography, affinity – affinity chromatography

Meta-analysis of mean bias and standard deviation

Mean bias (mean difference between POC and laboratory HbA_{1c}: POC HbA_{1c} − laboratory HbA_{1c}) and 2SD range of difference in HbA_{1c} between each of the POC devices and the laboratory test is presented in Figure 3.2. Results show large variability in bias in most of the devices. Even when mean difference (bias) was small within a single study, individual differences could be larger, as shown by the width of the two standard deviation bars in Figure 3.2. Pooling data on mean bias (Figure 3.3) in a meta-analysis shows that the majority of devices have a small overall mean bias; this was significantly non-zero for six devices (A1cgear, Quo-Lab, DCA and InnovaStar had overall negative mean bias and B-analyst and SDA1cCare had mean positive bias). Although the pooled mean bias for some devices was small across all studies, bias within a single device could vary substantially within studies as well as between studies. For example, as seen in Figure 3.3, mean bias across studies was −0.05% HbA_{1c} for the A1cNow device, but it varied from −0.70% (95% CI −0.82 to 0.58%)(79) to +0.67% (0.52 to 0.82%)(62). Similarly for studies of the DCA device, mean bias varied from −0.96% to +0.28%. Heterogeneity between studies in the main analysis was large for all devices, with an I^2 typically over 95%.

Summary estimates of the standard deviation of the differences (Figure 3.4) ranged from 0.21% for Cobas b101 which only included two comparisons to 0.53% for A1cNow which had 17 comparisons, though SDs from individual studies varied from 0.17% for Quo-Test (11) to 0.96% for A1cNow (88). The width of the prediction intervals show that for some devices the standard deviation of a future study could vary widely, with those for the A1cNow device ranging from 0.12% to 0.94%.

Sensitivity analyses

Risk of bias

The sensitivity analysis to exclude studies in which approximations were necessary during data extraction (Appendix 2, Figure A1) gave broadly similar results. Excluding studies at highest risk of bias (Appendix 2, Figure A2) resulted in the exclusion of more studies, meaning that the A1cgear device was no longer included; five devices with significantly non-zero mean bias remained in the analysis (Cobas b101, DCA, InnovaStar, Quo-Laboratory and SDA1cCare). The forest plot including only the eighteen studies which reported using an accredited laboratory for the comparator test in the meta-analysis is shown in Appendix 2, Figure A3. The A1cgear device dropped out of the analysis and, of those remaining, six devices had significantly non-zero bias: B-analyst, Cobas b101 and SDA1cCare had overall positive bias, whereas InnovaStar, Quo-Laboratory and Quo-Test had overall negative bias. Similar results were obtained when only studies using ion exchange chromatography laboratory methods were kept in the analysis (Appendix 2, Figure A4).

Figure 3.2 - Forest plot showing mean bias (in % HbA_{1c}) ± 2SD of HbA_{1c} measured using point-of-care devices compared with laboratory tests, by POC device, ordered by mean bias.

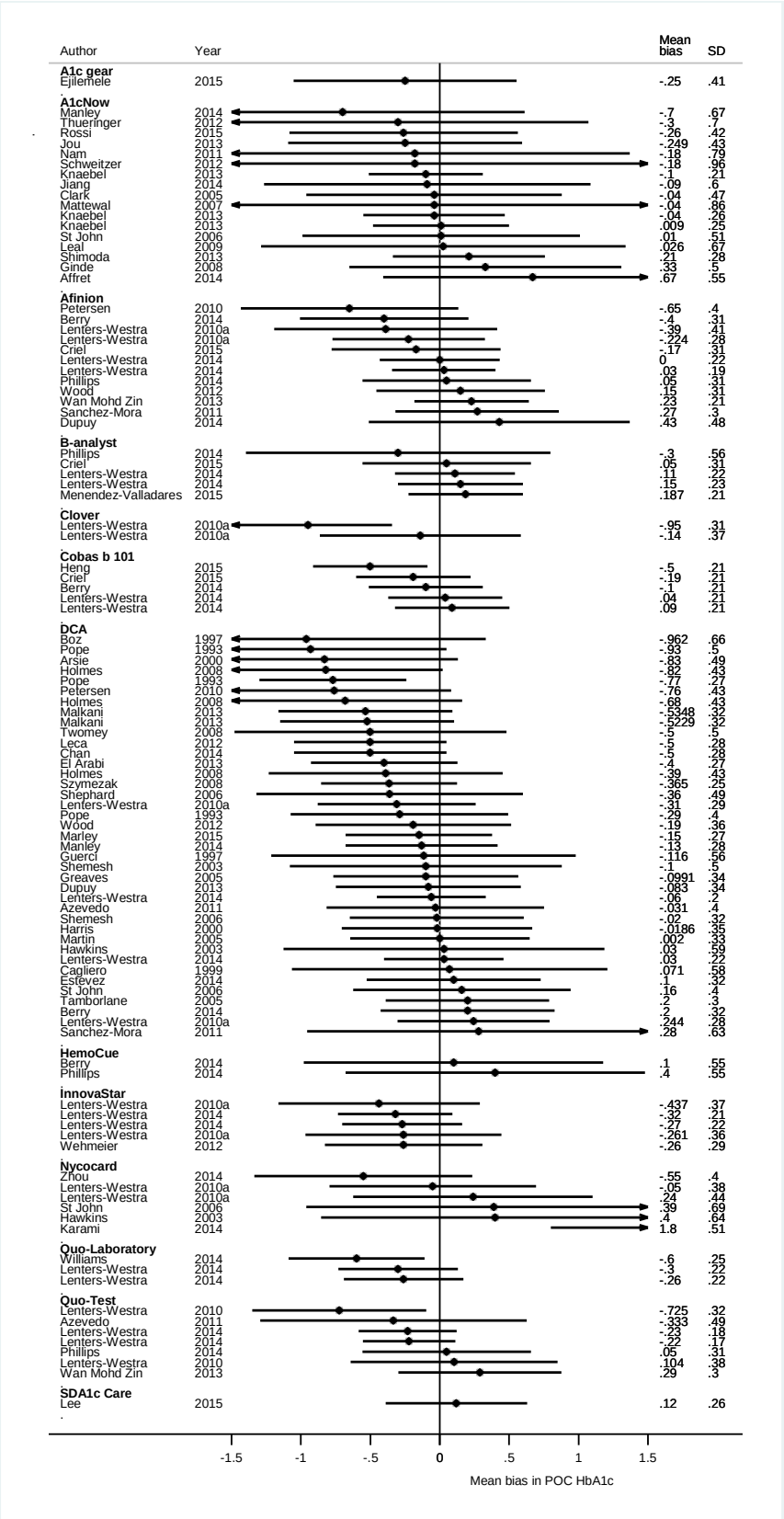


Figure 3.3 - Forest plot showing mean bias (in % HbA_{1c}) and 95% CI and prediction intervals, by POC device, ordered by mean bias.

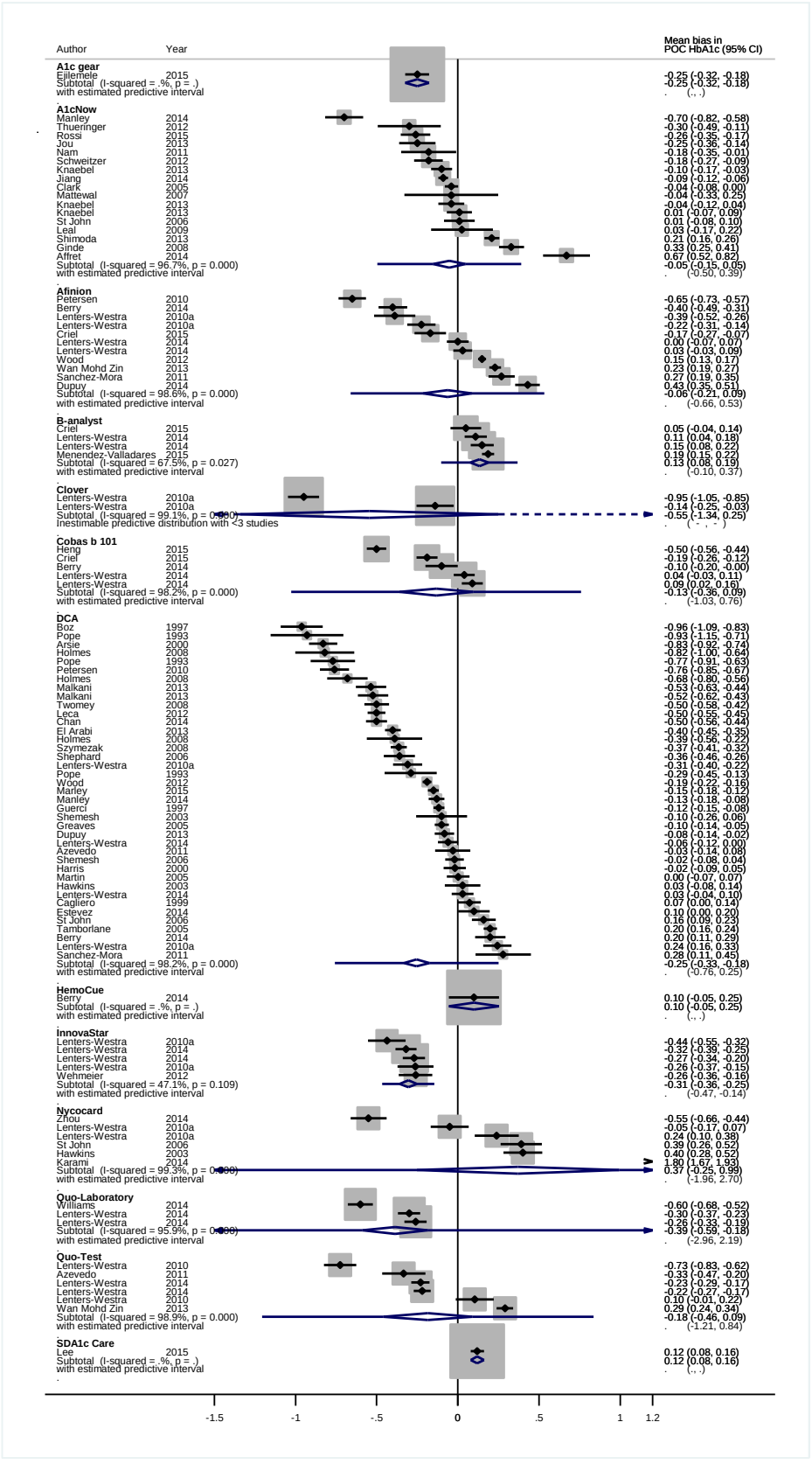
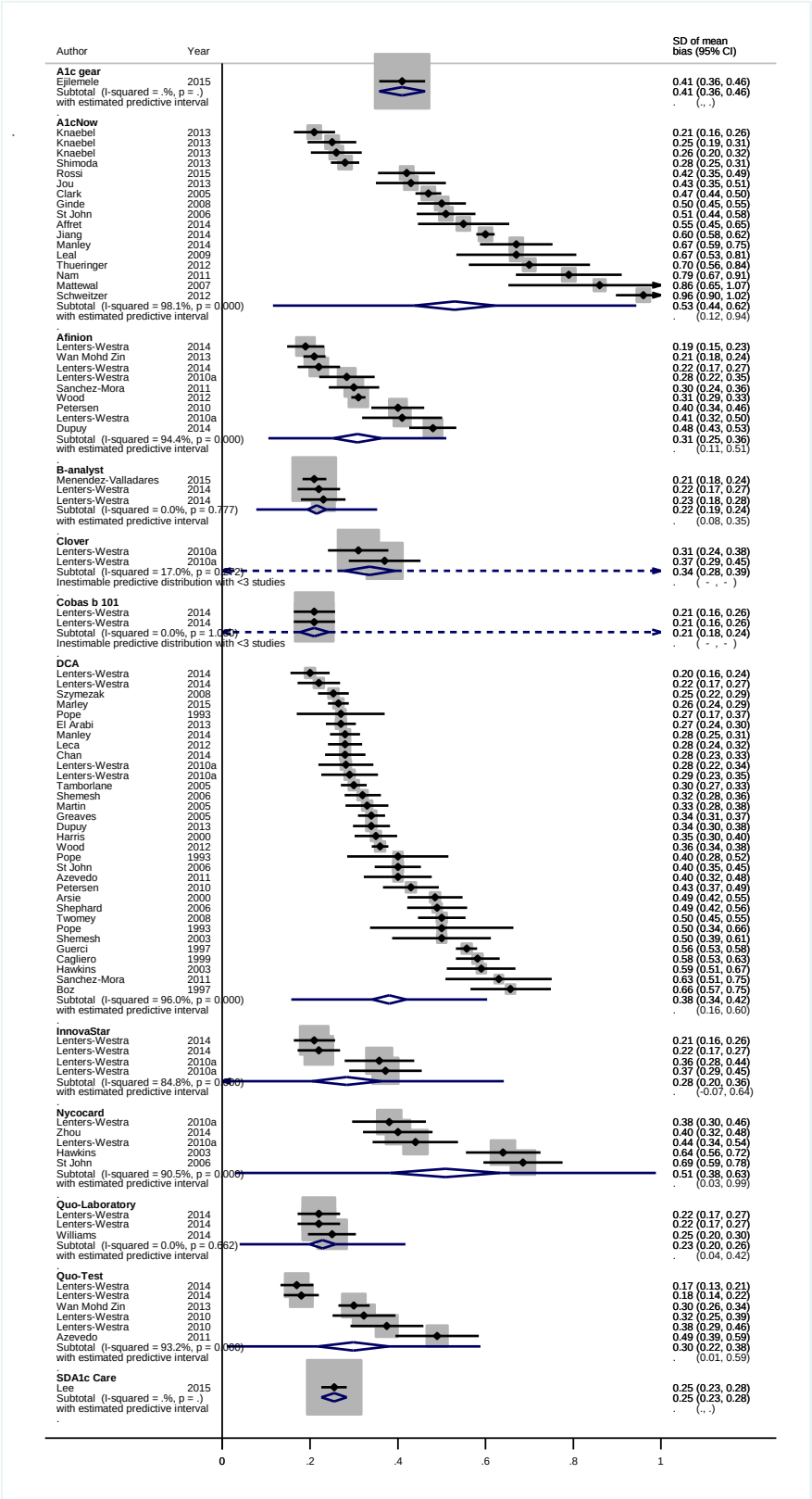


Figure 3.4 - Forest plot showing standard deviation of differences, 95% confidence intervals of SD and prediction intervals for included studies, by POC device, ordered by SD.



Changes over time

When the analysis was restricted only to studies published in 2014 and 2015 to minimise the effect of potential changes in cartridge calibration over time, all devices except the Clover device remained in the analysis (Appendix 2, Figure A5). Six devices still had significantly non-zero bias: A1cgear, InnovaStar, Quo-Laboratory and Quo-Test had mean negative bias, whilst B-analyst and SDA1cCare had mean positive bias. The DCA device had far fewer included studies and mean bias was no longer significantly negative. Heterogeneity between studies remained large in sensitivity analyses for all devices for which there were more than two comparisons.

Meta-regression

Using meta-regression, no evidence was found that year of publication significantly affected the mean bias for any of the devices, but there was a trend towards a less negative bias over time in the DCA device (coefficient 0.014% HbA_{1c} per year, p=0.081). A *post-hoc* meta-regression found that the standard deviation of the bias in the DCA device significantly decreased over time (−0.01% HbA_{1c} per year, 95%CI −0.015 to −0.006, p<0.0001). This suggests that the variability in measurements contributing to the mean bias in the DCA device is decreasing over time. A subgroup analysis to compare the size of the SD in 13 comparisons in studies published prior to 2006 with 19 comparisons in studies published between 2006 and 2015, found that those published in the most recent 10 years had a mean SD of 0.33% (95% CI 0.30 to 0.37) HbA_{1c} compared with a SD of 0.45% (95% CI 0.38 to 0.52) HbA_{1c} before 2006 (p=0.019).

Subgroup analyses

Setting

There were sufficient studies to enable a comparison of mean bias for studies carried out at different settings for only two devices, the DCA and the A1cNow. Subgroup analyses comparing clinical and laboratory settings found no difference in mean bias for either device. DCA: eighteen comparisons carried out in a clinical setting at point of care −0.27% (−0.38 to −0.16) compared with fourteen comparisons in a laboratory setting −0.30% (−0.47 to −0.14), p=0.963 (Appendix 2, Figure A6). A1cNow: eight comparisons carried out at a point of care setting 0.09% (−0.08 to 0.26) compared with three comparisons in a laboratory setting −0.27% (−0.76 to 0.23), p=0.144 (Appendix 2, Figure A7).

Operator

There were sufficient studies to enable a comparison of mean bias between different operators for only two devices, the DCA and the A1cNow. Mean bias in studies carried out by a laboratory operator was not significantly different from bias in those carried out by a clinical or other operator (defined as researchers, patients or pharmacist) in either the DCA or the A1cNow device. DCA: mean difference laboratory operator −0.30% (−0.47 to −0.14) versus clinical operator −0.30% (−0.42 to −0.18), p=0.956 (Appendix 2, Figures A8). A1cNow: mean difference laboratory operator −0.11% (−0.49 to 0.26) versus 'other' operator 0.05% (−0.12 to 0.23) (Appendix 2, Figure A9). A sensitivity analysis for the DCA device to exclude those studies in which estimates were made gave similar results: laboratory operator (−0.14%, −0.32 to 0.05) versus clinical operator (−0.36%, −0.56 to −0.17).

Other subgroup analyses

There was no difference in bias in 6 comparisons carried out in children −0.30% (−0.50 to −0.10) compared with 35 comparisons carried out in adults −0.24% (−0.33 to −0.16) on the DCA device (Appendix 2, Figure A10). There was no difference in mean bias between venous or capillary blood in either the A1cNow or DCA. A1cNow: venous 0.01% (−0.11 to 0.14), capillary -0.07% (−0.26 to 0.12) (Appendix 2, Figures A11). DCA: venous −0.24% (−0.40 to −0.09), capillary −0.36% (−0.50 to −0.22) (Appendix 2, Figure A12). The *post-hoc* subgroup analyses and meta-regression found no evidence of industry funding affecting mean bias in the Afinion and A1cNow devices (p>0.05). For the DCA device there was a significantly more negative mean bias in the studies with unclear funding status compared with those which reported industry funding (coefficient -0.275, p=0.022), but no difference between those reporting industry funding and those clearly not funded by industry (p>0.05).

Combining data from regression equations

Combination of data on mean bias at 6.5% (48mmol/mol), 7.5% (58mmol/mol) or 10.0% (86mmol/mol) HbA_{1c} cut-point thresholds from reported regression lines is shown in Table 3.3. For purposes of interpretation, I have taken biases of <0.2% HbA_{1c} to be low bias as this difference in HbA_{1c} values is not considered to be clinically significant. This data indicates that the A1cNow (12 studies) and Afinion (13 studies) have the lowest biases at cut-points of 6.5% and 7.5% with small negative bias of 0.1% HbA_{1c} or less and a negative bias of just over the 0.2% HbA_{1c} at a cut-point of 10% HbA_{1c}. DCA (32 studies) and Quo-Test (5 studies) both showed low levels of negative bias (<0.2% HbA_{1c}) at cut-points of 6.5% and 7.5% HbA_{1c}, and negative biases of just over 0.2% HbA_{1c} at a cut-point of 10% HbA_{1c}. B-analyst had small positive bias at 6.5% and 7.5% cut-points

which was slightly higher at 10% HbA_{1c}. Two devices, Clover and InnovaStar, performed poorly with large negative bias at all 3 levels of HbA_{1c}. Cobas b101, Nycocard and Quo-Laboratory had larger biases at cut-points of 6.5% and 7.5% than at 10% HbA_{1c}, for Cobas b101 and Quo-Laboratory this was a negative bias and for Nycocard this was a positive bias. Two devices, A1cgear and SDA1cCare, had only a single evaluation reporting the regression line, so although they appear to have acceptable levels of bias at all three HbA_{1c} levels they have not been considered further. There were no studies which reported the regression line equation for HemoCue.

Table 3.3 – Mean bias in HbA_{1c} (%) and SD at 6.5% (48 mmol/mol), 7.5% (58 mmol/mol) and 10% (86 mmol/mol) HbA_{1c} calculated from regression equations.

	Number of studies	6.5% (48 mmol/mol)	7.5% (58 mmol/mol)	10% (86 mmol/mol)
A1cgear	1	−0.19	−0.18	−0.15
A1cNow	12	−0.06±0.22	−0.10±0.29	−0.20±0.48
Afinion	13	−0.02 ±0.29	−0.08±0.35	−0.22±0.55
B-analyst	3	0.13±0.05	0.13±.05	0.27±0.05
Clover	2	−0.43±0.54	−0.48±0.55	−0.61±0.59
Cobas B101	3	−0.28±0.57	−0.24±0.68	−0.17±0.91
DCA	32	−0.12±0.25	−0.14±0.30	−0.22±0.46
HemoCue	0	-	-	-
InnovaStar	2	−0.25±0.07	−0.35±0.07	−0.55±0.07
Nycocard	5	0.44±0.80	0.33±0.85	0.12±0.86
Quo-lab	2	−0.3±0	−0.28±0.04	−0.15±0.21
Quo-test	5	−0.18±0.31	−0.18±0.33	−0.26±0.40
SDA1cCare	1	0.08	0.1	0.16

Combining data on precision

The mean precision, measured as CV for each analyser at low, medium and high HbA_{1c} as well as total CV, is presented in Table 3.4. Total CV for five devices, A1cgear, Afinion, B-analyst, Cobas b101 and Quo-Laboratory, was within the recommended threshold with a CV of less than or equal to 2%. The only device which had a CV ≤2% at low HbA_{1c} values was the A1cgear. At medium HbA_{1c}, five devices had a CV≤2%, A1cgear, Afinion,

Cobas b101, DCA and InnovaStar. Five devices had mean CV>2% at all measured levels of HbA_{1c}: A1cNow, Clover, Nycocard, Quo-Test and SDA1cCare.

Table 3.4 – Mean precision (CV in %) of POC devices at low (<6%, 42 mmol/mol), medium (6-8%, 42-64 mmol/mol) or high (>8%, 64 mmol/mol) HbA_{1c} calculated from raw values presented in % units.

	CV Low	CV Medium	CV High	Number of data points	Total CV
A1cgear	1.3	1.1	1.8	6	1.4
A1cNow	-	2.6	2.9	7	2.9
Afinion	2.5	1.6	1.9	23	2.0
B-analyst	2.1	-	1.2	3	1.5
Clover	4	-	3.5	2	3.8
Cobas B101	-	1.8	1.2	2	1.5
DCA	2.5	2.0	2.8	46	2.5
HemoCue	-	-	-	0	-
InnovaStar	3.2	1.2	2.4	4	2.3
Nycocard	4.2	5.3	3.5	5	4.2
Quo-lab	-	2.1	1.7	2	1.9
Quo-test	5.9	3.2	2.3	5	3.4
SDA1c Care	2.7	-	2.6	2	2.7

Diagnostic accuracy

Sufficient data were obtained to be able to carry out meta-analysis on diagnostic accuracy at the 6.5% (48 mmol/mol) cut-point for five devices (Afinion, DCA, A1cNow, Quo-Test and Nycocard). Sensitivity across all the devices was similar, ranging from 0.946 for the A1cNow to 0.990 for Nycocard. Specificity varied more, with the Afinion and DCA having the highest specificity of 0.997 and 0.990 respectively; the lowest specificity was 0.818 for Nycocard (Table 3.5 and Figure 3.5). All devices had a higher sensitivity than specificity, except the Afinion which had a higher specificity.

There were sufficient data to carry out a diagnostic accuracy meta-analysis at a cut-point of 7.5% (58 mmol//mol) for only 3 devices, Afinion, DCA and A1cNow. The sensitivity and specificity at this cutoff was lower for each of the devices at this higher threshold. The Afinion had a higher specificity than sensitivity.

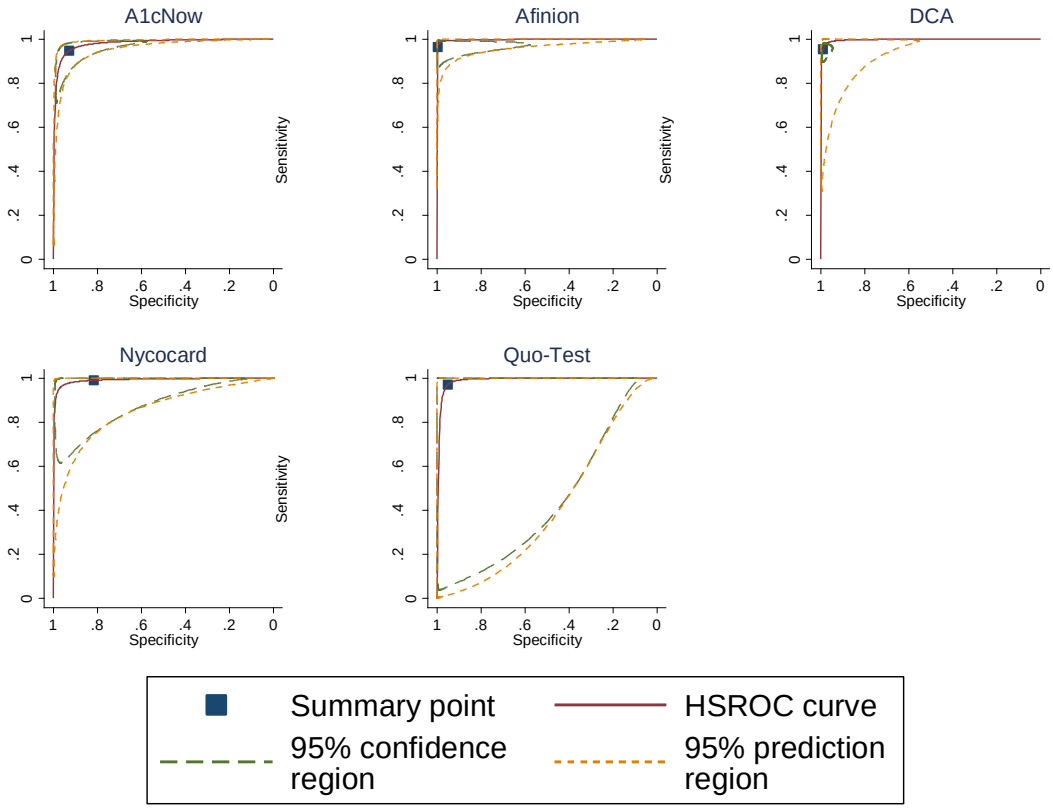
Risk of bias

Eighteen studies reported receiving funding from the point-of-care device manufacturers. In twenty-three of the included studies, the instrument was provided free of charge by the manufacturers. In nine studies it was unclear what the laboratory methodology was. Nine studies did not use a sufficiently wide range of HbA_{1c} concentrations to assess mean bias or regression line across all HbA_{1c} concentrations. Eighteen studies reported using an accredited or certified reference laboratory, but only nine studies could be confirmed to use a NGSP or IFCC certified laboratory for the comparator method.

Table 3.5 – Device sensitivity and specificity at 6.5% (48mmol/mol) and 7.5% (58 mmol/mol) from unpublished data, correlation and Bland-Altman plots.

	Number of studies	**6.5% (48 mmol/mol)**	
		sensitivity (95%CI)	**specificity (95%CI)**
A1cNow	9	0.946 (0.835-0.984)	0.928 (0.756-0.982)
Afinion	9	0.965 (0.910-0.987)	0.997 (0.910-1.000)
DCA	30	0.953 (0.913-0.975)	0.990 (0.964-0.997)
Nycocard	5	0.990 (0.939-0.998)	0.818 (0.472-0.957)
Quo-test	4	0.970 (0.792-0.996)	0.950 (0.776-0.991)
		7.5% (58 mmol/mol)	
		sensitivity (95%CI)	**specificity (95%CI)**
A1cNow	9	0.936 (0.858-0.972)	0.930 (0.897-0.954)
Afinion	9	0.912 (0.818-0.960)	0.982 (0.934-0.995)
DCA	29	0.902 (0.846-0.940)	0.975 (0.953-0.987)
Nycocard	-	-	-
Quo-test	-	-	-

Figure 3.5 - Bivariate hierarchical summary receiver operating characteristic plots showing sensitivity and specificity at 6.5% (48 mmol/mol) cut-points for A1cNow, Afinion, DCA, Nycocard and QuoTest.



3.3.5 Discussion

This meta-analysis compares the performance of POC HbA_{1c} devices with routine laboratory analysers by combining data from evaluations published in peer-reviewed journals. Data on mean bias, variability, bias calculated at different cut points using regression equations, diagnostic accuracy and precision were pooled using several different methods. Across all of the studies, nine of the thirteen included devices were found to have a net negative bias, meaning that the POC device reads a lower HbA_{1c} value than the laboratory measurement for blood samples from the same patient. Six devices had significantly non-zero mean bias; two with a positive bias, and four with negative bias.

Nearly all the devices exhibited large variations in standard deviation, so although the mean bias for a single device may be close to zero, there was large variability in bias both within and between studies, meaning that an analyser could read as much as 1% HbA_{1c} below to 0.4% above the true value across all the included studies.

In this piece of work, steps have been taken in an attempt to determine how sensitive the results are to changes in the analysis. This has been achieved through sensitivity analyses in which some evaluations were excluded to see how this impacted upon the result. Sensitivity analyses, to exclude studies in which aspects of methodology or reporting may have contributed to bias, were not found to substantially affect the results. Restricting the analysis to only include papers published in 2014-2015, resulted in the DCA device no longer having a non-zero bias. This may be an artefact of improvements in the cartridge calibration over time. Variability was lower when results were restricted to accredited laboratories only, particularly for the DCA and A1cNow devices. This may be because some of the comparator methods used in non-accredited laboratories, particularly immunoassays, show some bias or imprecision (105).

By combining data from regression equations, it has been possible to compare how mean levels of bias may vary across a range of HbA_{1c} levels. The results show that seven devices had low bias at HbA_{1c} values of 6.5% (48mmol/mol) and 7.5% (58mmol/mol). More importantly, five devices had high bias at the decision thresholds of HbA_{1c} 6.5% and 7.5%. In some cases, bias at these decision thresholds was higher than the bias at the high HbA_{1c} threshold (10% HbA_{1c}). High levels of bias at thresholds of 6.5% and 7.5% HbA_{1c} could affect diagnosis and treatment decisions for some patients, whereas a result 0.5% HbA_{1c} higher or lower than a laboratory measure of 10% HbA_{1c} may be less likely to result in a different choice of therapy. In order to understand how POC testing may affect potential decision making, a novel approach was used to combine data on diagnostic

accuracy to report sensitivity and specificity at thresholds of 6.5% and 7.5% HbA_{1c}. This has allowed the comparison of the efficacy of 5 different devices to accurately diagnose diabetes. These results show that the Afinion and DCA correctly categorise more patients at 6.5% HbA_{1c} compared with A1cNow, Quo-Test and Nycocard. Most devices had higher sensitivity than specificity, suggesting that they are better at ruling out diabetes. Only the Afinion device had a very high specificity, suggesting that this may be best to rule in diabetes.

There are some published data on bias at different HbA_{1c} levels: Leca *et al* (73) reported that there was greater bias at higher HbA_{1c} values in their evaluation of the DCA Vantage and Peterson *et al* found that the negative bias of the DCA Vantage and Afinion analysers increases at higher HbA_{1c}, from around 0.5% lower at HbA_{1c}<6% to around 0.9% lower at HbA_{1c}>7% (85), which is in keeping with our findings. A similar trend was observed by other researchers using the DCA 2000 (90, 106). Conversely, Wood *et al* found a lower bias for Afinion at HbA_{1c} between 8% and 9% compared with those outside these ranges, with the highest bias at less than 7% HbA_{1c} (107). The Cobas b101 has been reported to have a strong proportional negative bias at HbA_{1c} values>10% (101); this was not substantiated in our synthesis of 3 regression equations.

Many of the evaluations carried out in our review compared a capillary blood sample on the POC device, with a venous blood sample on the laboratory analyser. Although there may be slight differences in HbA_{1c} in different sample types (108, 109), it has been possible to eliminate this as a source of bias in two devices (A1cNow and DCA).

In order to demonstrate the variability in the measures, the mean bias was plotted along with a 2 standard deviation range to emphasise how much variation there was within a single study. This made it possible to demonstrate that, although the mean difference

within each study may be small, each data point contributing to it can vary widely. Variability within devices was also shown in precision data as not all the devices met recognised criteria for acceptable levels of precision (CV≤2% when HbA_{1c} is reported in % units (110, 111), or ≤3% if reported in mmol/mol units (112)).

Limitations

Although this systematic review included evaluations of the POC devices on any patient group or type of blood sample, there is a possibility that some of the studies may not have included the full range of HbA_{1c} values. Of the 69 studies included in this review, twenty-five reported the mean HbA_{1c} of the samples used in the evaluation, and fifty-three reported the full HbA_{1c} range. For this analysis, including a broad range of HbA_{1c} levels would be more important than inclusion of a large number of patients with a small range in HbA_{1c} levels, particularly for those studies which have derived a regression equation from their evaluation. Because this may have biased the results, studies which only considered non-diabetic populations, those that did not have a wide enough HbA_{1c} range or those that did not report the range in HbA_{1c} were excluded in a sensitivity analysis.

The data on mean bias and standard deviation have been pooled to give summary measures for each of the devices in the forest plot. Because of the large heterogeneity and small number of studies for some devices, the point estimate for the pooled bias has not been over-interpreted or discussed, but is used to highlight the direction and statistical significance of the effect. Instead, more emphasis has been put on the width of the confidence intervals and prediction intervals.

Some laboratory instruments have been reported to have systematic biases against gold standard methods (67, 105). This may have led to under- or over-estimation of biases in these studies, and thus affected the estimate of the bias in the meta-analysis; to illustrate

the uncertainty around the measures in this analysis, prediction intervals were included in the forest plots.

Only eighteen studies reported using an accredited laboratory to conduct the laboratory measurement. However, because the criteria for accreditation varies from country to country, this may not necessarily mean that laboratories undertook any quality assessment or were part of a quality assurance programme. Conversely, some laboratories may have been participating in quality assurance programs without laboratory accreditation or certification. Furthermore, the actual number of studies using accredited laboratories may be higher, as many of the papers included in this review were conference abstracts which were limited by word count. Only nine studies could be confirmed to use an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) or National Glycohemoglobin Standardisation Program (NGSP) certified reference laboratory.

Even though the intended end-users of POC devices are clinicians or healthcare workers, the majority of the performance evaluations included in this review were carried out in a laboratory setting by laboratory staff. The translatability of these laboratory evaluations to the clinical end-user in a point of care setting is therefore not known. It has, however, been possible to carry out subgroup analyses to examine the impact of operator and setting on bias for two devices, DCA and A1cNow, which found no difference in mean bias between a clinical and laboratory operator or between a POC and laboratory setting for either device. There were insufficient published data to enable comparison of performance between settings and operators for most devices; further evaluations in a clinical setting are now needed.

Mean values from duplicate POC tests were used by some researchers (87), this may have led to reported variability being lower than actual variability. In some studies it was not

clear whether results were reported as relative mean bias or absolute mean bias; however excluding these studies along with others with unclear reporting in a sensitivity analysis found similar results.

Equations for the regression line were used to calculate bias at different cut-points to enable comparison of levels of bias across a range of plausible HbA_{1c} values. Using these methods, it was not possible to take into account the scatter in the individual data points which contributed to the line. This data should therefore only be used as a guide to see how bias may differ at different HbA_{1c} values, and it is essential that the results be considered in the context of variability in the data, as shown in the forest plots Figure 3.2 to Figure 3.4.

Reports were only included in this review if they reported bias from Bland-Altman plots or regression equations. If precision data were reported in the included papers these were combined. As a consequence, we have been able to report CVs for the majority of the included devices, but this is by no means a comprehensive overview of precision of these devices.

Clinical implications

Because the majority of devices (nine of the thirteen devices) had an overall negative bias as well as large standard deviations, their use in a clinical setting may result in differences in treatment decisions compared with results from standard laboratory HbA_{1c} methods. POC HbA_{1c} results which are lower than laboratory methods may lead to under-treatment in some cases. The implications for overall patient care may therefore give rise to fewer short-term hypoglycaemic episodes; however the long-term use of POC testing may leave some patients exposed to higher than optimal levels of glycaemia. The long-term effects of this are not known, but studies have shown that even small increases in HbA_{1c} increase the

risk of micro- and macrovascular complications (113). Despite this, these risks may be outweighed by the other benefits of POC testing, including improved ability of the clinicians to make appropriate and timely treatment decisions (114, 115).

Devices with the lowest bias at HbA_{1c} thresholds ≤7.5% (58mmol/mol) may be preferred since large biases around decision thresholds for treatment may impact on diagnosis, prescribing and medication use. Lower precision and bias at HbA_{1c} values of 10% (86mmol/mol) is less likely to affect clinical decisions, as would bias closer to decision thresholds, and may therefore be of less clinical importance. The reproducibility or precision of a device is another crucial aspect of device performance, and should be considered in conjunction with bias. This analysis found that precision was variable, with the majority of devices having mean CVs greater than 2% at low HbA_{1c} levels (<6% HbA_{1c}, 42mmol/mol). Precision at medium levels of HbA_{1c} (6-8% HbA_{1c}, 42-64 mmol/mol) for most devices was better; this is arguably the most clinically important range because it includes key decision thresholds. Therefore sub-optimal performance in this range is more likely to impact on patient care. The data on precision which contributed to this analysis were collected by repeatedly analysing a single sample. This laboratory evaluation method is not representative of what happens in routine clinical practice, so although it is an important measure of instrument performance, its translatability to real-life device operation and decision-making is unclear.

This review has demonstrated levels of uncertainty which may be encountered from the analysis of multiple patient samples, which is more typical of a clinical context than a laboratory evaluation. These have shown that there is substantial variability in HbA_{1c} in most devices over a range of HbA_{1c} concentrations. The results illustrate a high magnitude

of variability in data from published evaluations; this is arguably the most important finding from this systematic review.

This meta-analysis contributes to the information available to clinicians who are considering which device to use. A test to measure HbA_{1c} levels must be accurate both near the diagnostic threshold of 6.5% (48mmol/mol), and at treatment thresholds of 7% (53mmol/mol) and 7.5% (58mmol/mol). However, accuracy across the whole therapeutic range is also important because these devices are likely to be used to monitor medication adherence and changing HbA_{1c} in those with established diabetes. The decision to select a suitable analyser must therefore be carefully considered, and be based both on clinical needs and acceptable bias and precision of the analyser. Moreover, the combination of instrument performance and biological variability in HbA_{1c} (11) could substantially affect the numbers of patients diagnosed with diabetes, and impact on clinical decision making for those with established diabetes. The NGSP now recommends that an HbA_{1c} test has to be within ±6% relative to the standard reference laboratory measurement (111). This analysis shows that only two devices failed to meet these requirements based on their mean measurement bias. However, because of the large variability observed within devices, it is probable that many of the devices will give some measurements greater or less than 6% of the patient's true HbA_{1c}.

The impact of using point-of-care HbA_{1c} testing on medication use, clinical decision making and patient outcomes now needs to be evaluated in a randomised trial with full economic evaluation.

3.3.6 Implications for this research

I have used the results from this chapter to help to inform which device would be most appropriate for use in the next stage of my DPhil. Briefly, this will involve placing three

HbA_{1c} point-of-care devices in three GP practices as part of a cohort study which is detailed in Chapter 4. For this study, I wanted to select a device which is easy to use; not requiring any sample preparation steps, required only a small sample size, thereby minimising pain from the finger-prick and blood collection, and has a short analysis time, meaning that time waiting for the result was not going to be a burdensome part of the consultation. In addition to these criteria, selecting a device with acceptable performance was crucial to the study, as I wanted clinicians to trust the results and base clinical decisions on the results. I therefore selected the Afinion device as it met the following criteria:

- Small sample size (1.5µl);
- Short analysis time (3 mins);
- Relatively well studied (several evaluations);
- Easy to use (no sample preparation steps);
- Small mean bias; and
- Variability smaller than other devices which had similar numbers of studies.

Reflections on this chapter and contribution of others

All the work conducted in this chapter was carried out by me; however some of the decisions on which analyses to include were made in collaboration with my academic supervisors and external collaborators. The systematic review reported in this chapter has been now been published in a peer reviewed journal (116).

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Chapter 4 : Feasibility study design and quantitative data collection

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4.1 Introduction

In this chapter, I report the design and results of a feasibility study to establish how point-of-care (POC) HbA_{1c} testing should be implemented in primary care consultations using the MRC's guidance for evaluating complex interventions (1), and have included components from a framework for evaluating the impact of new medical tests (2). The study rationale and theoretical framework are described, followed by the study design and methods used. Results on the demographics of the included participants, treatment pathways, operation of analysers, responses to questionnaires and other quantitative outcomes are presented. The implications of the findings from this study are used to focus the research questions in the qualitative element of this thesis in Chapter 5, and to aid the design of a future randomised trial outlined in Chapter 6.

4.1.1 Background and rationale

As highlighted in Chapter 1, trials of POC HbA_{1c} testing have, to date, failed to demonstrate an improvement in levels of HbA_{1c} (3), which may be an artefact of trial design, or because of recruitment of participants who were unlikely to benefit from this type of testing (4). The implementation of a new test in clinical settings can impact on the care pathway, which could affect health outcomes via many different mechanisms. Evaluating the impact of a new test should therefore incorporate an examination of the whole test-treatment pathway (2). Issues which need specific considerations when POC testing is introduced, include changes to timeframes for treatment decisions, changes in patient and clinician perceptions, and the impact on patient adherence. These may act individually, or in combination, to alter patient or clinician behaviour or clinical decision making, and could ultimately impact on patient health. Moreover a series of potentially confounding and modifying factors including technical feasibility (e.g. the location of the analyser and ease of integration into care pathways), technical performance and failures,

confidence in the result generated by the analyser, feedback of result to the patient, discussion of result with the patient, and action taken on the result in the patient appointment, have not yet been comprehensively addressed in trials.

A trial to test the efficacy of POC testing on health outcomes must be carefully designed to determine what could go wrong and optimise the delivery of the intervention and maximise the potential benefit. For the implementation of POC testing to be successful, adoption of new behaviours by clinicians who are delivering the intervention is crucial to ensure the result is acted on within the consultation (5). To achieve this, operational changes may be required, or delivery may need to be adapted between settings. POC testing comprises of a range of components which may affect outcomes or impact on effectiveness. Therefore, if results from a study or trial are negative, it is not clear whether it is because POC testing is inherently ineffective, or whether it simply had not been implemented correctly. The Medical Research Council (MRC) describes a complex intervention as an intervention consisting of several interacting components (1, 6, 7). The MRC's guidance for evaluating complex interventions entails a series of steps to establish whether an intervention works in everyday practice. These begin with identifying the evidence base, developing a theoretical framework, trialling the intervention in feasibility or pilot studies, evaluating in a large trial, and ultimately in full implementation. The distinction between feasibility and pilot studies is not always clear and these terms are sometimes used interchangeably. The NIHR has defined feasibility studies as those which collect data on important parameters that are needed to establish whether the main study can be done, whereas a pilot study is a miniature version of the main study (8). There is general consensus that the term 'feasibility' can refer to any preliminary work, but a pilot study includes design features of the main study which may include control groups or randomisation (9, 10). The preliminary steps of the MRC guidance involve determining

the mechanisms by which the intervention may improve health, exploring barriers to the successful application of the intervention, quantification of the potential benefit, and identifying patient groups who may respond best to the intervention (1, 7). The work presented in this chapter follows this guidance, and the framework for evaluating tests, to identify components which can affect the success of POC testing, and help to acquire a comprehensive understanding of what could go wrong.

Chapters 1 to 3 of this thesis have already provided an overview of the literature around POC testing, addressed current patterns in HbA_{1c} testing, and summarised the accuracy of POC HbA_{1c} devices. These have now been used to propose a theoretical framework, which identifies features deemed to be essential to POC testing, and outcomes which would need to be measured (Table 4.1).

It is central to POC testing that, if an action is to be taken on the test result, it takes place during the consultation rather than at a future time, or the benefits of the immediacy of POC testing are lost (5). When implemented correctly, POC testing will therefore change timeframes to treatment changes, and may affect clinical decision making.

The elements from Table 4.1 have been included in a study to inform whether POC testing can be delivered as intended and gather data on recruitment and acceptability. The study design does not include randomisation or a control group, and has therefore been defined as a feasibility rather than a pilot study. A key tenet of this study is that the test is administered, and the test result is acted on in a single appointment.

Table 4.1 - Theoretical framework – essential aspects of HbA_{1c} monitoring and behaviours which could impact on success of testing.

HbA_{1c} testing appointment	**Outcome measures**
• Patient attendance • Appropriate monitoring intervals • Test result reviewed by clinician • Appropriate medication prescribed • Patient collects prescription • Patient is adherent to medication	• HbA_{1c} test result • Medication changes • Patient understanding of diabetes and HbA_{1c} • Patient believing behaviour can affect outcomes • Patient satisfaction with care/treatment • Motivation and adherence to medication/appointments
Specific for POC testing:	
• POC test is administered during the consultation • Feedback of result and action taken on result in POC consultation • Adequate instrument performance • Streamlined care pathway	• Feedback of test result given during consultation • Advice/medication change given during consultation • Feedback from patients and clinicians in qualitative interviews • Technical failures • Location of analyser • Sequence of appointment • Satisfaction with POC testing • Patient appointment times
	Other outcomes which could be a barrier to POC testing:
	Costs to practice and patient Consultation time (patient) Care pathway

4.2 Aim

To establish which parameters need to be part of an POC HbA_{1c} testing consultation.

Overall objectives:

- To obtain data on patient recruitment, patient behaviour, consultation time, compliance, delivery of the intervention and views of surgery staff that will inform the design of a large-scale randomised trial.
- To describe care pathways and the experience of patients who have used POC testing, through observation, interviews and qualitative data collection using an extended and specific framework based on a model (2) designed to capture relevant data.

This Chapter describes the study design and methods for quantitative data collection in the first objective. The methods for collecting qualitative data are presented in Chapter 5.

4.3 Methods

This feasibility study took place in three GP surgeries in the Thames Valley area of the UK between May 2015 and April 2016.

4.3.1 Primary outcomes

Data on the following process measures were collected:

- Recruitment,
- Process of care,
- Consultation time and
- Delivery of the intervention.

4.3.2 Ethical approval

Full ethical approvals were received on 1st December 2014 by Office for Research Ethics Committees Northern Ireland (Research Ethics Committee Reference 14/NI/1127).

A substantial amendment was submitted to the ethics committee on 10th February 2015 to include additional questionnaire questions about appointment satisfaction. This was approved on 16th February 2015.

There were two protocol violations over the course of the study. Initially insulin treatment was one of the study exclusion criteria because most insulin-treated patients self-test their blood glucose levels and adjust their insulin dose accordingly. It was therefore felt that they would be less likely to benefit from point-of-care HbA_{1c} testing in terms of improvement in their HbA_{1c}. In October 2015 two insulin-treated patients were recruited in Woosehill surgery. After careful consideration, it was decided that it would be useful to

also get the perceptions and experiences of those who are insulin-controlled, since they are also potential end-users of point-of-care testing, and may have different needs or views from non-insulin users. The study sponsor and ethics committee were informed of the protocol violation and a second substantial amendment was submitted to the ethics committee on 27th October 2015 to extend the inclusion criteria to include patients who were insulin-treated. This was approved on 6th November 2015.

There were no ethical concerns with this study as there is a low risk of harms from this intervention. The University of Oxford lone workers policy was followed for qualitative interviews.

4.3.3 Patient and participant involvement

Two patient volunteers assisted in developing questions to append to an existing questionnaire with questions to capture features of the patient consultation which were specific to the study. Two patient representatives were included on the study steering committee.

4.3.4 Setting

The study took place across three GP surgeries to enable comparison between different centres in different locations. Two GP surgeries in Oxfordshire: Broadshires Surgery in Carterton and Bicester Health Centre in Bicester, and one GP surgery in Berkshire: Woosehill Surgery in Wokingham, agreed to participate in the study. Each centre was asked to recruit ten patients; with the aim of getting a range in patient age, ethnicity, education level, BMI and employment status. No incentives were provided to GP surgeries for participation, patient recruitment or follow-up. The study was first set up at Broadshires surgery where patient recruitment began two weeks before the other surgeries.

This ensured that any unexpected problems which may have arisen could be dealt with before full recruitment began.

4.3.5 Study management

Day-to-day management of the study was undertaken by myself, as Principal Investigator (PI), though some decisions were taken in consultation with a senior trial manager and trial coordinator. A management steering committee was set up which consisted of the PI, an academic GP, a senior trial manager, a trial coordinator and two patient representatives. The steering committee met on three occasions over the course of the study to monitor progress and resolve any issues which arose while the study was on-going. The meetings were held at the beginning of the study, after recruitment of the first patients, on recruitment of the final patient, and after the final study visit for the final patient.

4.3.6 Participant inclusion criteria

- Males and females of 18 years of age and over.
- Patients with a diagnosis of diabetes for at least 3 months.
- HbA_{1c} >7.5% (58 mmol/mol) who may require a treatment change and closer monitoring.
- Participants must be able to give informed consent.

4.3.7 Recruitment and timing

Patients were recruited in their GP surgery by the GP or practice nurse. Study participation time was six months during which time patients were asked to have three study visits in the GP surgery and, if consented, two interviews. A total of thirty patients were recruited to the study.

4.3.8 Identification of participants and informed consent

Eligible patients were identified by surgery staff based on recent laboratory HbA_{1c} results which indicated that their glycaemic control was sub-optimal (>7.5%, 58 mmol/mol). They were invited to participate in the study by the GP or practice nurse and provided with a letter of invitation and a participant information sheet. A minimum of 24 hours was given before participation was confirmed and informed consent was taken. Participants were given the option during the consent process to agree to be contacted by the PI to be invited for an interview. Each study participant was given a unique and anonymous identifying number which was used for all study materials.

4.3.9 Point-of-care (POC) analysers, cartridges and connectivity

The Alere Afinion AS100 point-of-care analyser was selected for use in this study for the reasons outlined in Chapter 3. Three analysers were purchased along with a bar-code scanner, printer and connectivity converter for each analyser. The analysers were delivered and set up in each of the GP surgeries along with a box of fifteen HbA_{1c} test cartridges. Training was provided by a representative from Alere for all clinical staff who were consulting with patients as part of the study; certificates were provided to those who had completed the training.

Cartridges were transported to surgeries in cool boxes with ice packs and transferred directly to a refrigerator. Cartridges were removed from refrigeration at least 10 minutes before using for analysis to allow them to reach room temperature. Unused cartridges could not be returned to the refrigerator, but could be stored at room temperature for up to 90 days.

Analysers in two of the GP surgeries (Broadshires and Bicester) were connected via a connectivity converter and a secure NHS Ethernet connection (OXNET) using Conworx™

software (for networking and management of POC devices) directly to the John Radcliffe hospital. An additional Ethernet port had to be installed in the nurse's room at Bicester surgery to allow this connectivity. Analysers were all set up to require an operator log-in prior to operation and a patient identifier. Each operator was provided with a unique bar code which they scanned each time a sample was run. Patient identifiers were typed in manually as the patient NHS number in Broadshires and Bicester surgeries to allow synchronisation of date and time of test and HbA_{1c} test result with the patient's electronic hospital records. Results were then automatically uploaded back to GP records overnight. At Woosehill surgery the patient study ID was used as the patient identifier. Results were manually transcribed to the case report forms.

No quality control (QC) procedures were followed over the course of the study as each of the analysers and each batch of cartridges had been QC checked in the John Radcliffe hospital laboratory before being sent out to the surgeries. Each surgery was provided with a high and a low HbA_{1c} manufacturer's control solution for testing and were free to test these as frequently as they wished.

4.3.10 Questionnaires

All recruited patients completed four questionnaires both at the baseline visit and at the end of the study. These questionnaires were selected with a view to comparing satisfaction, knowledge of diabetes, motivation to self-manage and medication adherence before and after receiving POC testing (see Appendix 3 for copies of questionnaires):

- Diabetes Treatment Satisfaction Questionnaire (DTSQ) (11) appended with additional questions specific to this study to capture experience of the medication and consultation (DTSQ+).
    - DTSQ consists of 8 questions relating to medication and treatment

    - Appointment Satisfaction Questionnaire - appended questions relate to understanding of HbA_{1c} and satisfaction with their clinic visit and time.

- Revised Illness Perception Questionnaire (IPQ-R) (12, 13) to capture patients' perceived level of, and responses to illness.
    - Four-page questionnaire about symptoms, feelings about diabetes and causes of diabetes.
- Patient Activation Model (PAM) (14) to capture level of motivation to self-manage their diabetes.
    - Ten questions about confidence to manage diabetes.
- Morisky Medication Adherence (MMAS) (15) to measure levels of adherence to medication.
    - Eight questions relating to adherence to taking medications.

4.3.11 Study procedure

Clinicians involved in the study were asked to complete a short survey at the start and end of the study. The survey captured details of job type (GP, nurse or healthcare assistant) and consisted mainly of multiple choice or tick boxes with some free text answers and space to give more detailed feedback if needed on expectations or concerns of POC testing. Around 5 minutes was allowed for completion of the survey.

Patient study visits were organised as follows and summarised in the patient flow chart (Figure 4.1):

Visit 1 – Patient recruitment and baseline data (around 45 minutes)

- Eligibility assessed.
- Informed consent taken.
- Venous blood sample taken for laboratory HbA_{1c} baseline measure.
- Measurement of height and weight.
- Case report form (CRF) completed and patient demographics recorded.
- Patient given DTSQ+, IPQ-R,PAM and MMAS questionnaires to complete whilst in the surgery and hand to receptionist for posting.

A sub-set of up to 15 patients were interviewed before their first POC appointment (See Chapter 5).

Visit 2 – 12 weeks after baseline visit (around 20 minutes)

- POC HbA_{1c} test performed.
- Result fed-back and discussed with the patient.
- Based on the test result, lifestyle or treatment options discussed.
- CRF completed with details of total patient appointment time, sequence of consultation (care pathway), POC HbA_{1c} test result, medication changes or advice given.
- MMAS questionnaire completed.

Visit 3 – 24 weeks after baseline visit (around 30 minutes)

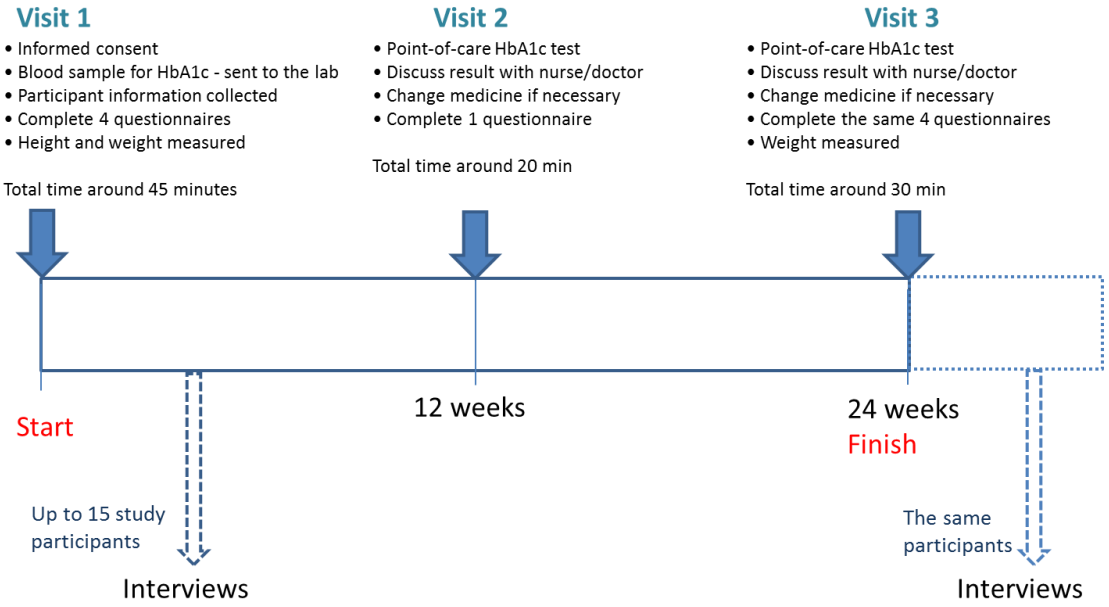
- POC HbA_{1c} test performed.
- Result fed-back and discussed with the patient.
- Based on the test result, lifestyle or treatment options discussed.

- CRF completed with details of total patient appointment time, sequence of consultation (care pathway), HbA_{1c} test result, medication changes or advice given.
- Measurement of weight.
- Patient completed DTSQ+, IPQ-R, PAM and MMAS questionnaires.

The same group of patients were interviewed for a second time on completion of the study (see Chapter 5).

During the first study visit patients provided a venous blood sample for laboratory analysis of baseline HbA_{1c}. This meant that those patients who were interviewed had not yet experienced POC testing, which meant it was possible to capture expectations in the interviews.

Figure 4.1 - Patient study timeline.



4.3.12 Data collection and analysis

Demographics and baseline characteristics of study participants were collected on patient sex, age, ethnicity, diabetes duration, smoking status, level of education, body mass index and people living in the same household, using a CRF at visit 1.

Data from the POC consultations in visits 2 and 3 were collected on location of the POC analyser, the sequence of consultation, clinical decisions made during the consultation and length of POC appointments were collected using CRFs. Problems encountered with analyser operation and cartridge failures were reported by surgery staff running the tests and recorded.

Mean and standard deviation (SD) HbA_{1c} were summarised at baseline, visit 2 and visit 3, mean (SD) BMI was summarised at baseline and visit 3, numbers of medication changes and advice given at both POC visits were tabulated. Length of appointments for both the POC visits were summarised in the text and differences between surgeries discussed.

Data on problems encountered during the study, including connectivity of analysers, uploading results, protocol deviations and incomplete follow-up were recorded. Explanations for the problems encountered were sought through discussion with surgery staff.

4.3.13 Analysis of questionnaire results

Diabetes Treatment Satisfaction Questionnaire, DTSQ (11)

Scores of 0 to 6 were given for each question, where 0 represents very dissatisfied and 6 represents very satisfied. Questions 1, 4, 5, 6, 7 and 8 were added to get a total score for the DTSQ between 0 and 36. Questions 2 and 3 were treated separately to give perceived frequency of hyperglycaemia and hypoglycaemia respectively. T-test was used to assess

whether differences between scores were significant; statistical significance was set at p-value <0.05.

Revised Illness Perception Questionnaire, IPQ-R (12, 13)

Items were separately added together to get scores for: Identity, Timeline, Consequences, Personal control, Treatment control items, Illness coherence items, Timeline cyclical, Emotional representations and Causes.

Coding for identity scale yes = 1; no = 0. Other items were scored: strongly disagree =1, disagree =2, neither agree nor disagree = 3, agree = 4, strongly agree = 5; a reverse score was applied to questions: IP1, IP4, IP8, IP15, IP17, IP18, IP19, IP23, IP24, IP25, IP26, IP27, IP36

High scores on the identity, timeline, consequences, and cyclical dimensions represent strongly held beliefs about the number of symptoms attributed to the illness, the chronicity of the condition, the negative consequences of the illness, and the cyclical nature of the condition. High scores on the personal control, treatment control and coherence dimensions, represent positive beliefs about the personal level of control of the illness and a personal understanding of the condition. T-tests were used to compare scores between baseline and visit 3; statistical significance was set at p-value <0.05.

Patient Activation Model, PAM (14)

Questionnaire answers for each question were scored as disagree strongly = 1, disagree = 2, agree = 3 or agree strongly = 4. Scores were averaged for each participant at baseline and endpoint. Scores are interpreted as follows:

Score	Patient characteristics
1	Does not understand that they need to play a role in their health
2	Lacks basic knowledge about their condition, treatment options and care
3	Has the basic facts about their condition and some confidence in some aspects of their condition
4	Had changed behaviour to manage condition

Morisky Medication Adherence, MMAS (15)

Comprises of eight questions with Yes/No answers. Each Yes scores 1, and No scores 0, except question 5 where scores were reversed.

Score of 0=high adherence, 1 or 2 = medium adherence, >2 low adherence

4.4 Results

4.4.1 Recruitment and compliance

Thirty patients were recruited to the study between 7th May 2015 and 26th October 2015. Patients were recruited to the three GP surgeries as follows:

Broadshires, Carterton: 14

Bicester Health Centre: 11

Woosehill Surgery, Wokingham: 5

Baseline visit questionnaires were not returned by one study patient from Broadshires surgery. All five patients at Woosehill surgery only completed study visit 1 and study visit 3 due to unmanageable workload issues encountered by the GP at that site during the study. One patient recruited in Bicester surgery withdrew before the second study visit. A reason for withdrawal was not provided. The remaining 24 patients completed all three study visits and questionnaires.

4.4.2 Demographics

Demographics of the recruited patients is shown in Table 4.2. Approximately equal numbers of men and women were recruited to the study. Mean age was 57.8 years (range 30 to 79 years), the majority of patients were white and two were Asian, mean diabetes duration was 6.7 years and mean BMI was 32.2 kg/m^2 (ranged 25.1 to 40.7 kg/m^2). There was a range in educational attainment and most patients lived with a partner.

Table 4.2 - Demographics of recruited patients.

Sex	14 female, 16 male	
Age (years), mean (range)	57.8 (30-79)	
Ethnicity	28 white, 2 Asian	
Diabetes duration	6.7 ± 4.3 years	
Smoking status	17 former smokers 13 never smoked	
Highest level of education	7 University 10 College 13 Secondary school	
BMI (kg/m^2) Mean±SD (range)	32.2±3.5 (25.1 to 40.7)	
Living in the same household, n	Alone Partner Other family>18 Children<18	3 25 9 5

All patients reported regularly attending eye and foot checks.

4.4.3 Delivery of the intervention and feedback of results

One patient was not able to receive a POC test result at the second study visit because the analyser gave error messages at three attempts before the nurse took a venous blood sample for laboratory analysis of HbA_{1c} instead. The issue was eventually identified as a faulty batch of cartridges which may not have been stored correctly prior to delivery to the surgery. This was rectified by replacing the cartridges with a new batch and carefully following storage instructions.

In all cases feedback of results to patients was reported as taking place on the case report form.

4.4.4 Description of HbA_{1c} in study participants

HbA_{1c} was non-significantly lower at the end of the study compared with baseline (p=0.45) (Table 4.3). Results were similar when only patients with full follow-up data were included in the analysis.

Table 4.3 - Mean (SD) HbA_{1c} at baseline and follow-up visits.

	Visit 1 (n=30)	**Visit 2 (n=23)**	**Visit 3 (n=29)**
HbA_{1c} (%)	8.21±0.98%	8.09±1.44 %	7.93±1.19 %
HbA_{1c} (mmol/mol)	66.3±10.7	64.9±15.7	63.2±13.0
BMI (kg/m^2)	32.2±3.5 kg/m^2	-	32.6 ±3.6 kg/m^2

4.4.5 Operation of analysers and connectivity

There were a total of 11 cartridge failures and error messages over the course of the study (Table 4.4). Nine of these were resolved by replacing two boxes of cartridges. These problems were attributed to incorrect storage at the John Radcliffe Hospital in which there may have been removal from refrigeration during their storage. These 9 failures are therefore not considered to be due to inherent problems with the cartridges or incorrect storage by the GP surgeries. The other error messages were caused because there was too little time between the cartridge being removed from refrigeration to running the sample meaning the cartridge was still too cold, and too little blood on the cartridge.

Download of patient results and synchronisation with hospital records was demonstrated to be feasible by inputting the patient's NHS number into the analyser.

Table 4.4 - Table of cartridge failures during the study by surgery.

	Broadshires (n=34)	**Bicester (n=25)**	**Woosehill (n=5)**
Cartridge batch problems	5	4	0
Not enough blood	1	0	
Cartridge too cold	0	1	0
Total failures	**6**	**5**	**0**

4.4.6 POC appointment and clinical decisions

The clinical decisions made during the POC consultations are summarised in Table 4.5. Results were only acted on during the nurse-led consultations in Broadshires and Bicester surgeries. No treatment changes or lifestyle advice was given in Woosehill surgery. However, during qualitative interviews with patients and clinicians, it transpired that some patients had continued to receive diabetes care from a nurse who was not directly involved in the study whilst the study was ongoing, and two patients had recently received a medication change during these nurse appointments.

Table 4.5 –POC appointment and clinical decisions made during POC consultations.

	Visit 2 (n=23)	**Visit 3 (n=29)**
Mean±sd POC HbA_{1c} (mmol/mol)	64.9±15.7	63.2±13.0
Results fed back to patient	23	29
Result discussed with patient	23	29
Action taken:	12	18
Medication change	5	7
Lifestyle advice	7	11
Mean appointment time in minutes (range)	24.1 mins (15-45)	20.1 mins (10-35)

No action was taken on the POC test result in any of the GP-led consultations. The 5 GP-led consultations were significantly shorter than the 48 nurse-led consultations (11.4±0.9 versus 23.8±7.7 minutes) ($p<0.001$).

4.4.7 Questionnaire results

The aggregated DTSQ score was high at baseline (score of 29.6 of a maximum score of 36) suggesting that most patients were satisfied with their current diabetes treatment. There was however, a statistically significant increase in treatment satisfaction at visit 3 compared to baseline ($p=0.03$) (Table 4.6). There was no difference in perceived risk of hyperglycaemia or perceived risk of hypoglycaemia between visit 1 and visit 3. Sixteen patients were more satisfied with their treatment at visit 3 compared with baseline. Eight

patients were less satisfied with their treatment at visit 3 than at baseline. There was no significant difference between any of the aggregated appointment satisfaction scores between the baseline visit and visit 3 (Table 4.7).

Table 4.6 - Diabetes Treatment Satisfaction Questionnaires, DTSQ.

	Baseline	Visit 3	p
Satisfaction with treatment	29.6±4.4	31.5±3.9	0.03
Perceived hyperglycaemia	3.2±1.8	3±1.9	0.79
Perceived hypoglycaemia	1.2±1.7	0.9±1.4	0.66

Table 4.7- Appointment satisfaction questionnaire (DTSQ+).

	Mean score (from scale of 1-6)		N with higher score	N with lower score
	Baseline	Visit 3		
Understanding of why HbA_{1c} is measured	Yes – 27 No – 1 Not sure - 1	Yes – 26 No – 2		
Importance of immediate result	5.1±1.6	5.4±0.8	7	7
Importance of having time to discuss result	5.7±0.6	5.9±0.4	4	2
Knowing HbA_{1c} would help managing diabetes	True – 25 Not sure - 4	True – 25 Not sure - 3		
Satisfied with time spent with HCP	5.9±0.4	5.8±0.5	1	6
Satisfied with advice from HCP	5.8±0.5	5.8±0.5	3	5
Satisfied with continuity of care	5.6±0.7	5.6±0.6	5	6
Satisfied with discussion with HCP	5.6±0.6	5.6±0.8	4	5
Satisfied felt understood by HCP	5.6±0.6	5.5±0.9	6	7
Satisfied with information from HCP	5.4±1.2	5.7±0.6	6	6
Satisfied with personal treatment by HCP	5.8±0.4	5.8±0.4	3	5
Satisfied with time spend with HCP	5.6±0.7	5.7±0.5	7	5
Satisfied with appointment today	5.9±0.3	5.8±0.4	3	6
Understanding of maintaining good control	No – 0 Yes – 26 Not sure - 1	No – 1 Yes – 25 Not sure - 2		
Is diabetes well controlled now?	No – 5 Yes – 15 Not sure - 6	No – 5 Yes – 17 Not sure - 6		

HCP – Healthcare professional

Results from the revised Illness Perception Questionnaire are shown in Table 4.8. High scores in identity, timeline, consequence and timeline cyclical (highlighted in grey in Table 4.8) suggest strongly held beliefs about the number of symptoms attributed to the illness, the chronicity of the condition, the negative consequences of the illness, and the cyclical nature of the condition; whereas high scores in personal control, treatment control and coherence represent positive beliefs about personal control and understanding. Although there was a trend towards a lower score in identity, indicating that fewer symptoms were perceived to be associated with their diabetes, there was no significant difference between any of the illness perception scores between baseline and visit 3 (Table 4.8).

Table 4.8 - Illness perception questionnaire IPQ- R.

	Baseline	**Visit 3**	**p**
Identity	3.2±2.5	2.3±2.9	0.21
Timeline	24.0±5.1	25.0±4.3	0.42
Consequences	18.6±4.1	19.7±4.5	0.33
Personal control	23.7±3.9	25.1±4.1	0.18
Treatment control items	18.8±2.6	18.2±2.5	0.37
Illness coherence items	19.1±3.7	19.6±4.3	0.63
Timeline cyclical	9.5±3.3	9.8±3.2	0.72
Emotional representations	16±5.1	15.4±5.9	0.68
Main causes (scoring≥3)	Hereditary, diet or eating habits, my own behaviour & aging	Stress or worry, hereditary, diet or eating habits & my own behaviour	

The mean PAM score was between 3 and 4 at baseline, suggesting that most patients were already in possession of the facts about their condition and had confidence to manage some aspects of their diabetes. Those with the highest scores above 4 were already playing a part in managing their diabetes. Patient activation was therefore already very high at baseline and there was no significant difference between mean PAM scores at baseline

and visit 3. There were, however, 17 patients who had a higher PAM score at visit 3 than at baseline, compared with six patients who had a lower PAM score (Table 4.9).

Table 4.9 - Patient activation measure, PAM.

	Baseline	**Visit 3**	**p**
Mean PAM score ±SD	3.2±0.4	3.3±0.4	0.12
Range in scores	2.6-4.7	2.4-4	
Number of participants whose score went up	-	17	
Number of participants whose score went down	-	6	

Two patients were diet-controlled before starting the study and did not complete the MMAS questionnaire. Medication adherence scores suggest that medication adherence was low to moderate throughout the study. There were no significant differences between mean MMAS scores at baseline and visit 3. Eleven patients had lower MMAS scores at visit 3 compared with baseline, suggesting that these patients may have improved adherence to their medication. Five patients had higher MMAS score at visit 3 than baseline suggesting lower adherence. Ten patients had identical scores at baseline and visit 3 (Table 4.10).

Table 4.10 - Morisky Medication adherence questionnaire, MMAS.

	Baseline (n=27)	**Visit 2 (n=24)**	**Visit 3 (n=29)**	**p**
Mean score ±sd	2.2 ± 1.8	2.0 ± 1.7	2.0 ± 2.0	0.20

4.4.8 Location of POC analyser and care pathway

In all cases, the POC analyser was located in the nurse or GP's office. In the nurse-led appointments, the POC test appointment replaced the regular blood-taking and subsequent consultation. In the GP-led consultations, the GP carried out the consultation in addition to the patients' routine diabetes visits with the nurse. Participants were only seen by the nurse or GP and had their HbA_{1c} test in the consulting room, meaning there was no requirement to leave the office.

4.4.9 Length of POC consultations

Mean (±SD) appointment time in visit 2 was 24.1±6.2 minutes, compared with 20.1±6.0 minutes for visit 3. In study visit 2 the appointment length ranged from 15 to 45 minutes. One appointment lasted 60 minutes because three cartridges failed and a venous blood samples was then taken. One appointment lasted 45 minutes because two cartridges failed before the third one worked to give a result. The next shortest appointment time was 35 minutes.

4.4.10 Clinician survey results

Five clinicians completed a survey at the start of the study, before using POC testing. They were all positive to very positive about POC HbA_{1c} testing. Two clinicians felt it was likely to be worth the extra cost, whereas three felt it would be too expensive. Other free text comments related to the perceived benefit in its use for educating, informing and motivating patients. Two clinicians wanted clarification on who would pay, and one wanted information on accuracy compared with traditional lab data.

All four clinicians who completed a survey at the end of the study reported that the analyser was easy to use. They all reported to have very positive feelings about POC testing and believed it to be accurate. Opinions on convenience to clinicians ranged from very convenient to less convenient. Feelings about the effect on patient care ranged from ‘no difference’ to ‘improved care’, and feelings about cost ranged from ‘some concerns’ to ‘too expensive’. Suggested benefits of POC testing were that the instant result could promote positivity between healthcare professional and patient, and reduced anxiety to patient waiting for the result. One clinician said QC requirement was a concern and another said the space the analyser took on the desk was a problem.

4.4.11 Problems encountered when implementing this study

A direct connection via an Ethernet port was required to connect the analysers directly via the OXNET system at the John Radcliffe Hospital in two surgeries. This would allow results from the analysers in the GP surgeries to be uploaded to the patient's hospital records. The nurse's office in Bicester surgery did not have a spare Ethernet port available therefore, after agreement with the Practice Manager, an additional port was installed to enable full connectivity of the Afinion.

Study patients' 10-digit NHS numbers were typed into the analyser by the nurses in Broadshires and Bicester so that the patient's HbA_{1c} result would synchronise with their hospital records. The hospital systems at the John Radcliffe Hospital in Oxford usually use the patient's medical record number (MRN), which is shorter than an NHS number, for all laboratory tests carried out in the hospital. Because patients in primary care do not necessarily have an MRN number, it was not possible to use this for the POC tests. Initially the hospital database did not register the patient's NHS number because it was too long, but this was rectified by the hospital IT team.

The second study visit did not take place for five patients recruited in Woosehill surgery. Correspondence with the GP involved in the study revealed that this was a result of excessive workloads in the surgery caused by staff shortages coinciding with an inspection. The work burden of the GP involved in the study was prohibitively high at the time and the GP was unable to find time to schedule visit two appointments for all five of the study patients, meaning they missed a study visit.

4.4.12 Collaboration with hospital laboratory

This work was conducted in collaboration with the point-of-care team at the John Radcliffe Hospital in Oxford. All the analysers were delivered to the hospital where they

were checked prior to being distributed to the GP surgeries. In addition, all cartridge lot numbers used in this study had been quality checked in the hospital before use in the surgeries. On completion of the study, the hospital Point-of-Care Manager had costed a full service to GP practices who want to adopt POC HbA_{1c} testing in their practice. They would provide full training on analyser operation, QC and QA service as well as analyser connectivity for the Afinion analyser. Cartridges would be purchased through the hospital at £6.30 per cartridge for HbA_{1c} (inclusive of VAT, QC, QA and connectivity). They explained that they would also support C-reactive protein (CRP) testing on the Afinion analyser at a cost of £5.24 per test.

4.5 Discussion and conclusions

4.5.1 Summary and key findings

This feasibility study of POC HbA_{1c} testing in 30 patients across three GP practices, found that the POC test result was fed back to patients in 100% of consultations and clinical decisions were made in 58% of the consultations. Appointment duration ranged from 10 to 45 minutes, but clinical decisions were only made during consultations of 15 minutes or longer.

Despite emphasising that the POC appointment should replace regular appointments and be used to make clinical decisions, this did not always take place in the study. No action was taken on the POC test result in one-third of all the POC test results despite some patients still having HbA_{1c} over 7.5% (58 mmol/mol) in their appointment.

Results indicated that nurses were able to successfully perform testing and base treatment decisions on results within the 20 minute routine consultation time. However, the POC HbA_{1c} testing was not correctly implemented in one site, where GP appointments ran alongside the usual care appointments in which clinical decisions were made. This may be

due to longer consultation times, and thus fewer time constraints in nurse consultations; this needs to be explored further in qualitative interviews. There were five missed appointments in one site when staff workloads were high.

The process of performing the test was correctly carried out in all consultations, but incorrect storage of cartridges led to a number of error messages necessitating repeat testing. It was demonstrated that test results could be successfully uploaded and synchronised with patient hospital records using patient NHS numbers via a secure Ethernet connection. Clinicians reported that they found the analyser easy to use, but all the clinicians expressed some concern about the costs of POC testing.

4.5.2 Strengths of this work

Three sites were selected in two different counties serving different populations which enabled the comparison of GP-led versus nurse-led consultations. This feasibility study has provided an understanding of patient recruitment rates, drop-out rates and likelihood of complete follow-up, technical feasibility, patient care pathways, appointment times and clinical decision-making, whilst using POC HbA_{1c} testing. It has also provided an opportunity to explore possible reasons for incomplete follow-up, or failure to act on the POC result, which will be useful in improving future study designs. Having the support of the hospital team benefitted this study by enabling connectivity, transfer of results to patient records, and bar-code scanning for operators. Moreover, this collaboration made the logistics of implementing this type of testing easier, and demonstrated the viability of close involvement of POC hospital teams in the management, training and QC for POC testing in primary care. This could provide a realistic model for GP practices wishing to adopt POC testing in both allowing full connectivity and synchronisation of results with patient records, whilst relieving surgery staff of the burden of training and QC, which could be a barrier to adoption of POC testing (16).

4.5.3 Comparison with the literature

There are few examples of studies which have explored how POC testing can be integrated into patient consultations. The UK primary care-based study (4) found that the results of POC HbA_{1c} testing for diabetes monitoring were not always used to make clinical decisions in the POC appointment. Crocker *et al* found that using the DCA Vantage for HbA_{1c} or lipid testing in a US primary care setting resulted in fewer tests overall being performed, and thus may lead to potential cost savings (17). However, cost reimbursement structures differ greatly between the US and the UK; therefore these savings may not be seen in UK primary care. Another US-based study used POC INR testing for monitoring warfarin therapy (18). The investigators found that introducing the POC testing alone did not improve the proportion of people in range, but used in conjunction with computer software to assist with dose adjustments, it did improve time in therapeutic range. In other settings, POC creatinine testing in community pharmacies in The Netherlands was found to be feasible and resulted in improved management of patients (19).

Adoption of new technologies is important if they improve patient care. POC INR testing has been well embedded in UK primary care with around 43% of GP practices reported to use it compared with 17% using POC HbA_{1c} testing (20). These differences in rates of adoption of POC testing for INR compared with HbA_{1c} may be related to the demonstrated clinical and cost effectiveness of POC INR testing (21). The consequences of receiving a delayed result for a laboratory INR may be life-threatening, whereas an out-of-range HbA_{1c} is less likely to have acute clinical consequences. Therefore, the more widespread adoption of POC INR testing may be linked to its demonstrated improvement in patient outcomes. A report published in 2014 (22) found that adoption of new

innovations by GPs was likely to be influenced by NHS policies and incentives as well as ease of adoption and access to information from other doctors or NICE guidance.

In addition to adoption of the technology, acting on the result must take place for the patient to benefit. Work in this thesis has found that in some cases the result was not acted on. This failure to act, also called clinical inertia, has been estimated to affect around 25% of diabetes patients who may not have had their treatment appropriately adjusted (23). This widespread problem leaves patients exposed to suboptimal glycaemic control suggesting that initiatives are needed to improve diabetes management.

POC testing has been linked to improved medication adherence, communication with healthcare professional and engagement of patients (24, 25). Health beliefs, including a perceived positive relationship with physician, are strongly associated with diabetes medication adherence (26, 27), suggesting that those with a better understanding of the implications of their condition were more likely to be adherent to their medication. Modification of health beliefs has also been shown to be linked to an improvement in HbA_{1c} (28). Moreover, there is evidence that those who are aware of their HbA_{1c} are more likely to have a better understanding of diabetes and how to manage it (29).

4.5.4 Limitations

There are several limitations to this work. The three GP practices in this study were practices which had previously participated in research and expressed a strong interest in participating in the study. All three GP surgeries were located in relatively rural settings with low levels of deprivation compared with other parts of the country. This is likely to have resulted in recruitment of a selected group of patients, for example, none of the patients were current smokers and only two non-white participants were recruited to the study. GP practices in urban settings may differ in terms of patient proximity and ease of

access to the surgery, as well as numbers of ethnic minorities, levels of deprivation, lifestyle behaviours or health-care seeking behaviours of patients. There may be other implementation issues in these settings which could not be explored in the current study. It is recognised that the population recruited to this study is unlikely to be truly representative of those with diabetes across the country, which may limit the generalisability of the findings from this work.

Recruitment rates were slow in some practices. Data were not collected on numbers of eligible patients or numbers who were invited to join the study, so this could not be reported quantitatively.

At each of the sites, only a single clinician was using the analyser, meaning that finding a convenient location to situate the analyser was straightforward. It is recognised that locating a POC analyser in a setting with multiple users would require more thought; siting the analyser in a different location to the patient consultation could impact on patient flow and waiting times.

The questionnaires used in this study were selected to measure behaviour change, but because study participants were already very satisfied with their usual care, there was little room for improvement. For those measures which did show a statistically significant change, it is unclear whether the change was clinically important (30). Self-reported scales such as the MMAS medication adherence scale can have poor sensitivity and specificity and may be biased by false reporting by patients (31). The ability of the questionnaires to measure change may therefore have been limited; however, questionnaires have been used in previous research to detect changes in behaviour resulting from an intervention (32, 33). Using qualitative methods would help to better understand how POC testing may have impacted on behaviour change (34).

This study was not powered to detect clinical outcomes such as change in HbA_{1c}, nor was follow-up long enough to examine long-term health outcomes such as hospitalisations, cardiovascular events or death. These would need to be addressed in a larger, longer-term randomised trial.

4.5.5 Issues to consider in future studies

Although there were 11 cartridge failures during the study, the majority of these were attributed to incorrect storage of the cartridges prior to delivery and are thus not thought to reflect the true performance of correctly stored cartridges. This is, however, an issue which could affect the uptake of these technologies.

The two nurses who participated in this study and operated the point-of-care devices were both diabetes-specialist nurses whose responsibilities included making treatment decisions and medication changes. If clinical staff who perform the test are not able to make treatment decisions, then the process of care may require the patient to see multiple members of staff, and may result in longer consultation times.

Patient recruitment rates were slow, with only 30 patients recruited over a five-month period across the three GP surgeries. This may, in part have been because the three practices started recruiting patients on different dates, and recruitment of the 5 patients at Woosehill surgery did not take place until the fifth month. Moreover, there was incomplete follow-up of patients in Woosehill surgery which may have been improved through incentivising the surgeries. Financial incentives to practices for patient recruitment and follow-up may be something to consider including in a future study to boost recruitment rates.

Ensuring that members of surgery staff who usually provide diabetes care have easy access to the analyser is crucial. Though, to be able to take full advantage of the benefits

of POC testing, it is also important that the analyser is accessible to other staff members. This would allow HbA_{1c} tests to be performed for patients who do not have a scheduled diabetes appointment. Locating the analyser in a convenient and accessible location to allow all potential users to run a sample is an important consideration to get the full benefit of these technologies and to minimise disruptions in patient flow.

Connectivity of POC analysers to enable download of results direct to hospital laboratory databases and synchronise with hospital records has proved to be feasible and successful. Although the process of synchronising results with hospital records was feasible, this did require involvement of the POC team and IT staff at the JR hospital. If POC testing were to be implemented in other health authorities, there may be similar issues which would first need to be addressed. This may require some time commitment from hospital IT and laboratory staff if full integration with hospital records is sought. A system to generate bar codes either from patient MRN or NHS numbers would facilitate this process and allow nurses or doctors to scan patient identifiers instead of manually entering 8-digit NHS numbers which is cumbersome and prone to error.

Quality control is an area which was barely touched upon in this study, and may need to be carefully considered in a future study. There are not currently any QC schemes in place via national quality control bodies such as NEQAS (National External Quality Assessment Service) or WEQAS (Wales External Quality Assessment Scheme) for POC testing as there are for laboratory testing. QC issues for POC testing differ from laboratory methods because there may be lot-to-lot variability in cartridge calibration. It is possible that many central laboratories with active point-of-care teams would want to take this on to ensure results generated from POC tests are consistent with lab results.

Adoption of POC testing could lead to changes in clinician behaviour, and provide opportunities to test patients who are not frequent attenders, but may present at the surgery with other health issues; however, there are risks of over-testing with POC technologies. How this impacts on behaviour and utilisation of tests and overall costs of HbA_{1c} testing will therefore need to be established.

4.5.6 What has been learnt from this research

The GP-led appointments were less likely to have resulted in medication change which may have been related to appointment duration rather than the clinician conducting the consultation. Typically GP appointments are time-restricted and pressures to keep to a 10-minute consultation may be too high to allow optimal implementation of POC testing. The nurse-led appointments were typically about twice as long as the GP appointments (20-25 minutes compared with 10-12 minutes). This time pressure may be a key factor in the successful implementation of POC testing which will be explored in qualitative interviews. A future trial should be designed to separately analyse data generated by GPs compared with nurses, as well as compare outcomes with appointment length and other indicators of surgery time pressures such as time in waiting room and time to get an appointment.

For this intervention to be successful, the POC appointments should fully replace usual monitoring, possibly with the exception of the annual test in which multiple markers are monitored. The act of performing the POC test could be carried out by any trained clinical member of surgery staff, but the consultation to discuss and act on the result should be carried out by the clinician who usually carries out the HbA_{1c} monitoring in diabetes patients.

In qualitative interviews, covered in detail in the next chapter, some patients mentioned that the time to complete the four questionnaires was burdensome. Questionnaire

completion had not been piloted in advance, but, on reflection, would have been useful, and has been noted for future study planning.

4.5.7 What next?

The ability to measure changes in behaviour using questionnaires was limited because the majority of people were already satisfied with their care at the baseline visit. Any preferences now need to be explored using qualitative interviews. Additionally, qualitative interviews may help to provide explanations for the missed study visits, and to understand the perceptions of clinicians who carried out the study appointments. These have been addressed in the qualitative element of this study covered in Chapter 5.

Findings from this study have now been published in the journal, Diabetes Research and Clinical Practice (35).

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Chapter 5 : Understanding experiences, facilitators and barriers to POC HbA_{1c} testing

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5.1 Introduction

This chapter reports the methods and findings of the qualitative interviews carried out as part of the feasibility study, the design and quantitative results of which have been reported in Chapter 4. In this chapter, I endeavour to understand patient and clinician views on point-of-care (POC) testing with a particular emphasis on if, and how, POC testing may have affected behaviour, and seek explanations for some of the study outcomes. I will give a rationale for the methods used, and present the design, methodology and results of the qualitative research. These will include methods to recruit participants, collect data, and conduct the qualitative analysis. Findings from the qualitative interviews are presented and discussed in the context of the literature along with the implications for future research.

Prior to commencing this work, I attended courses on qualitative research methods and training for NVivo software for qualitative data analysis. I worked closely with my academic supervisor during the analysis and sought advice from another qualitative researcher with expertise in thematic framework analysis.

5.1.1 Mixed methods research

A combination of qualitative and quantitative methods has been used to answer the research question in the feasibility study. The quantitative strand forms the majority of the work and is given priority in the overall interpretation of results since feasibility of implementation, and impact on patient recruitment and decision-making, are key to the intervention. The qualitative strand was used to explain some of the quantitative findings, understand the processes and explore differences across contexts (1); these findings can be used to generate hypotheses which can be explored in future work. This does not, however, lessen the importance of including a qualitative element to this research to understand perceptions and attitudes to POC testing which may influence behaviour,

uptake, implementation and adherence. Mixed methods are commonly used in implementation research as they can provide an understanding of reasons for success or failure of the intervention (2). Fully capturing measures of behaviour, experiences and perceptions is not possible using measurement scales or other type of quantitative data collection (3). Qualitative methods, on the other hand, can be used to harness multiple viewpoints and complex issues which can arise with some interventions (4). This study uses an embedded design, in which the qualitative strand is embedded in the quantitative study, allowing opinions and experiences of patients to be collected at different time-points over the course of the study (5). Results from this qualitative work can then be used to complement, explain and corroborate findings from the quantitative data collection (4).

In this study, qualitative data were collected from patients twice: initially prior to receiving the intervention, and again at the end of the study, in order to capture expectations, experiences and any changes in views or behaviour. Clinician views were also sought at the end of the study. The qualitative and quantitative strands of this research have been carried out assuming that there is an interaction between these strands, meaning that the overall interpretation of qualitative data from the feasibility study will be based on a framework from the quantitative data (5). The qualitative element has been used to explain some of the quantitative findings and inform the design of future work in this area. The use of this design should make it easier to identify and understand which key elements are required for POC HbA_{1c} testing so these can then be implemented in a future study.

5.1.2 Literature review and rationale

Findings from previous qualitative studies have already been summarised in Chapter 1. To date only a single study explored views of POC HbA_{1c} testing in a primary care setting in the UK (6). Nurses and GPs interviewed in that study felt that having the result available

for discussion with the patient was a strong advantage. However, the usefulness of the result may depend on the nurses' responsibilities and ability to make management changes. These qualitative interviews were part of a trial (7) in which some clinicians found it difficult to change usual care processes and did not act on results in the consultation, but continued to see patients twice. As discussed in Chapter 1, for patients to benefit from POC testing, results must be acted on during the POC consultation (8). Therefore, built into the design of the feasibility study outlined in Chapter 4, was the pre-requisite that the POC test result should be fed back to the patient during the POC consultation and that clinical decisions or action taken on the test result should take place within that consultation. On this basis, the study reported in this chapter differs from the previous study by reporting the expectations and experiences of patients whose HbA_{1c} is measured using POC testing in their GP practice, as well as clinicians' views of POC HbA_{1c} testing.

5.1.3 Aims and objectives

This work aimed to understand patients' views on POC HbA_{1c} testing and the POC consultation. This will include convenience to patients, whether it helped them to engage with their diabetes or care, and whether it may have resulted in behaviour change. Overall the objective of the qualitative element to this research is to identify aspects of the intervention which are most likely to succeed and those which may need to be changed. It is also possible that the qualitative interviews will raise further questions which need to be answered in a future study, for example in identifying whether there may be certain patients for whom the intervention is better suited.

5.2 Methods

5.2.1 Sampling framework

The sample from which to select participants for this qualitative study was limited to those recruited to the feasibility study. Because this work aims to explore the barriers and facilitators to POC testing, it is important to identify as diverse a group of patients to recruit to the qualitative study as possible to capture as full a range of views as possible within the available sample. Purposeful sampling is commonly used in implementation research and can be used to get a maximum variation sample to explore shared patterns as well as unique views and diversity (2). After receipt of documentation from the first study visit, patients who had consented to be contacted were therefore invited for interview by purposeful sampling within the sampling framework (9). The selection criteria were based on age, ethnicity, sex, highest level of education, people sharing the household and BMI, with the aim of getting the broadest range in perspectives. This should ensure that patients with a range in levels of motivation, knowledge and understanding of diabetes, working people versus retired, and different support networks at home were interviewed, to maximise the generalisability of the findings across settings or populations (2).

5.2.2 Interview guide

Patient and participant involvement

Interview questions were developed in consultation with patient groups. A meeting was held with two patient volunteers who provided feedback on general topics to cover during patient and clinician interviews. A list of interview topics was developed, and approved by the volunteers in a second consultation. Prior to commencing the study, these topics were presented to a panel of patient volunteers at a meeting organised by the Thames Valley and South Midlands NIHR Clinical Research Network to get further feedback.

5.2.3 Data collection

Patients were contacted by phone to invite them for interview. If they agreed, then a time and place convenient to the patient was arranged for the interview which could be at their home, place of work or another quiet location. Each invited patient was interviewed twice; the first was timed after the first study visit and before the second study visit. The second interview took place after the third study visit when the quantitative data collection part of the study was complete and all forms had been returned.

Before starting the interview, it was explained to the patient that the interview would be audio-recorded, transcribed and anonymised. Each patient was then asked to provide written informed consent to be interviewed. Interview guides were semi-structured; a list of questions was prepared in advance and used as a guide during interviews (Appendix 4: interview schedule). The order of questions was revised as interviews progressed and some questions varied between interviews. To explore patient responses further, additional questions were asked in response to some replies (10). Where possible, questions were open-ended to allow participants to give their own views.

Six specific subject areas which were deemed to be particularly relevant to point-of-care testing were identified prior to the interviews because of their potential impact on care or behaviour (11-14). These were satisfaction with care, understanding of HbA_{1c}, views on POC testing, adherence, convenience and behaviour. These topics were covered in all interviews; however, any other ideas which emerged during the interview were explored in subsequent interviews.

In the interviews which took place before POC testing, questions focussed on knowledge and understanding of HbA_{1c}, the effect of diabetes on health, attitudes to testing, appointment length and understanding and expectations of POC testing. In interviews after

POC testing, questions focussed on process of POC appointments, convenience, experience and views of POC testing. The second interview included some of the same questions as the first to make it possible to pick up changes in responses, views or behaviour and questions specific to experience of POC testing were also asked. Themes which had arisen during the first interview with that patient, which may have been about care or behaviour, were re-introduced in the second interview to explore these further. This allowed views and experiences of the POC consultation to be compared with those before the patient had experienced POC testing.

All interviews were recorded on a digital voice recorder as MP3 files. After the interview these were uploaded to a computer directory with restricted access and transcribed verbatim by an external transcriber approved by University of Oxford. Any references to names or places were anonymised. Once received, each of the transcripts was checked to ensure that it corresponded with the MP3 recording and corrected as necessary.

At the end of the study, one clinician from each of the three sites was interviewed to get their perspectives of using POC testing. The purpose of these interviews was to get a better understanding of operational issues and process of care, such as sequence and timings of appointments, and location of the POC device. Questions were also asked on the effect of POC testing on the clinical consultation and feedback, such as discussing the result with the patient, and making immediate clinical decisions based on the result. Questions posed to the clinicians are shown in Appendix 4. This was used as a guide, and further questions were added as necessary to explore some points in greater depth.

5.2.4 Coding and qualitative data analysis of patient interviews

A thematic framework analysis was used to analyse the interview data (15, 16). This method was selected because it provides a structured approach for organising data from

qualitative interviews and analysing the data. It differs from many types of qualitative data analysis in that it can be based on an *a priori* framework, which may be informed by previous research findings making it a more deductive approach. However, new topics which emerge from the data can also be incorporated into the framework (17).

All interview transcripts were uploaded into QSR NVivo version 10 software for coding. Patient interviews were coded once both interviews for that patient had taken place, and the second interview transcript had been received from the transcribers. Data from both interviews with each patient were kept together and both transcripts were coded in sequence to retain the linked nature of the interviews for each participant. This ensured that any perceived changes in behaviour, views or perceptions of POC testing between the first and second interview were picked up. Deductive coding with the main themes in mind was used, though open, inductive coding was also used to ensure that other aspects of the data were captured for future hypothesis-generating analyses and any other relevant themes were picked up.

The pre-determined themes used in the thematic framework analysis of patient interviews related to advantages and convenience, disadvantages and barriers, and behaviour, informed by a framework for introducing new tests (18). As the study progressed, concepts emerged which were relevant to the study and were inductively added to the framework. The final analysis of patient interviews was restricted to five themes which were influenced both by the research objectives of the feasibility study; to optimise the implementation of POC testing into general practice, and also following a framework for evaluating tests (18). These topics were: advantages, behaviour, visibility, barriers, and explanations for some of the study outcomes.

Once coding was complete, codes were grouped into related topics, and then topics which fitted into the framework themes were grouped together under the relevant theme. Charting of the data was carried out using Microsoft Excel; each theme was labelled as a separate tab in an Excel spreadsheet. Data for each patient was kept together with separate columns for patient ID, code, then verbatim text retrieved from NVivo codes into separate columns for the first interview and second interview as appropriate. An example of the charting process used for the framework analysis is shown in Table 5.1 below.

During the data analysis, any patterns or relationships which emerged in the data were explored to see whether differences in patient responses could be explained by patient demographics or other patient-specific factors which became apparent during the interviews. Specifically, age and whether the patient was working were considered when analysing responses.

Table 5.1 - Example of charting process.

Theme –advantages			
Patient ID	**Code**	**Interview 1**	**Interview 2**
Patient 1	One appointment	everything is compacted into one visit, you know is easier	I think having everything all in one go is a big advantage
	Immediate result	So it is more up to date …	you know everything's there and it's in front of you …
Patient 4	One appointment	yeah it's going to be fantastic for me personally, … I just need one appointment there instead of two.	The immediacy of the results and that having that conversation all in one go would be a huge time saving.

5.2.5 Coding and analysis of clinician interviews

The three clinician interviews were coded together at the end of the study. For these, all aspects of POC testing were analysed using a framework based on: advantages of POC

testing, disadvantages of POC testing, impact on clinical decision making, and practicalities and patient flow. Analysis of the clinician interviews was carried out in a similar way to patient interviews by grouping codes into themes and using NVivo to copy verbatim text into an Excel spreadsheet. Verbatim text from patient and clinician interviews which most clearly illustrated the theme was presented in the results.

5.2.6 Rigour

Measures taken to minimise researcher influence on data collection included involvement of patient groups in devising the interview questions and asking open questions where possible to allow the interviewee to express their own views. Rigour in the coding process was ensured by having a random sample of coded transcripts double-checked by a senior qualitative researcher. The analysis process was carefully documented and descriptions of any findings supported by verbatim quotes in the report (19). Even though the data collection and analysis were based on a framework (18), it is acknowledged that my pre-conceived ideas will have had some influence on the way the data were collected, analysed and interpreted. To minimise the potential bias from this, I presented results to a group of senior qualitative researchers to get feedback. I remained aware throughout the analysis of pre-conceived ideas and checked the codes and themes to ensure I had not only selected items which confirmed my ideas.

5.3 Results

5.3.1 Summary of patients

A total of fifteen patients were interviewed; demographics of patients interviewed are presented in Table 5.2 showing that a varied sample was recruited in terms of age, BMI, duration of diabetes and education. Eight patients were female; age range was 30 to 70 years; BMI ranged from 28.2 to 40.7 kg/m^2; duration of diabetes ranged from 1 year 10 months to 20 years; two patients were Asian, the remainder were white; highest level of

education was secondary school for five participants, college for five patients and university for five patients; eight patients were in paid employment, and two were insulin users.

Table 5.2 – Demographics of interview cohort.

Female/Male	8/7
Mean age	56.9 year (range 30-75)
Mean BMI	32.4 kg/m^2 (range 28.2 – 40.7)
Duration of diabetes	7.7 years (range 1.83-20)
Ethnicity	13 white 2 Asian
Highest level of education	Secondary school – 5 College – 5 University or higher - 5
Number in paid employment	8
Insulin use	2

Patient interviews lasted an average of 30 minutes each, but ranged from 8 minutes to 53 minutes. The three clinician interviews with two nurses and one GP lasted between 14 minutes and 27 minutes.

5.3.2 Thematic framework developed from coding reports

Patient interviews

Results are presented in a framework of factors which may influence the adoption of POC testing and mechanisms by which it may influence behaviour change. The themes and associated codes are shown in Table 5.3.

Table 5.3 – Thematic framework.

Theme	**codes**
Convenience	Convenience, working, distance to doctors, one appointment more convenient
Barriers to POC testing	Barriers, concerns, accuracy, cannot see the point, test failures
Behaviour and motivation	Being watched more closely, Reinforcement for good behaviour, motivating, adherence
Immediacy of result & visibility	Can link changes in HbA_{1c} back to recent behaviour, more visible, would like graph, reinforces behaviour, printout, waiting for result in usual care stressful, getting result
To understand reasons for deviation from protocol:	
Experiences of study to learn from	HCP likes POC test, wanted to use test, POC test should be used by usual care provider, nurse appointments longer, prefer nurse appointments
New theme:	
Frequency of testing	Frequency of testing, better behaviour with more frequent appointments

5.3.3 Findings from qualitative interviews

Advantages of POC testing & convenience

During patient interviews, the convenience of POC testing featured as one of its main advantages. Overall, patients viewed POC testing to be more convenient; an important aspect of this was having a single appointment instead of two appointments, which fitted in better with people's family lives and meant that they did not have to take time off work to attend appointments.

Elaine, 50, who does not work but has school-age children, explained that she viewed the convenience of having one appointment as one of its main advantages.

"I couldn't say that I could see any disadvantages; I just think the fact that everything is compacted into one visit, you know is easier." [before POC testing]

"It isn't an issue no. I think having everything all in one go is a big advantage. You know, going in for your blood test, then going back to discuss it, you know from a personal point of view it's time consuming." [after POC testing]

Younger people who were working and had young families highlighted the advantages of the time-saving element of POC testing. Gita, 35, who has very young children and works nights observed that it would be easier to fit one appointment into her busy life.

"In this world it is really worse. In this busy world. People don't have much time for. It's not only this thing we have got to look at. People have lots of other things to do. So there is just one appointment and can make everything and the machine gives an accurate result which is perfect." [after POC testing]

Daniel, 47, who works 12 miles from his GP surgery and has children living at home, similarly viewed time saving to be a big advantage.

"The immediacy of the results and that having that conversation all in one go would be a huge time saving." [after POC testing]

Paul, 55, who had to retire recently for medical reasons mentioned that booking appointments and follow-up appointments can be a nuisance.

"But with a point of contact it doesn't really matter because you just book the appointment when it's required, go in and it's done; you don't have to worry about booking an appointment for the blood and then…it's the, it's the messing around getting the extra appointment… That's the real [um] drag." [after POC testing]

Barry, 59, has had diabetes for nearly 8 years and, although his employers are fine about him taking time out of work for his appointments, he felt that the POC test appointments fitted into working life much better.

"Well yeah I mean I've got no problem [um] if it's during work time, there's no problem there, but it's just, you know it's always best to have to go to the doctors one less time I suppose." [before POC testing]

"Oh it's fantastic this…you didn't have to make another appointment…. No, no time off work, it's there instantly….It's a fantastic idea I think." [after POC testing]

Sunita, 56, works nights and feels that she is always in a rush after work to get to her appointments.

"Yeah, yeah. Yeah especially for me because I have to go straight [um]…because I've just done a nights; I have to get ready, showered and then go to get the [um] appointment done." [after POC testing]

When asked about preferences for future HbA_{1c} testing, responses ranged from those that had no preference at all and would defer to whatever the clinicians deemed to be best:

"It's actually, you know I feel whatever's got to be done has got to be done and that's it." [P19, M, 72 years, after POC testing]

to very strong preferences for POC testing:

Interviewer: "OK so you would [um] prefer to have a test like this?"

Patient: *"Oh yes definitely…Definitely yes. So, rather than going and take all this…take all the…fills it out and what have you, and then being sent off and then waiting a week to get the answer…Oh yeah it's much…definitely much better.*" [P72, F, 70 years, after POC testing]

Motivation to improve behaviour

The effect of POC testing on perceived motivation to manage behaviour, attend appointments and control diabetes, was a major theme which emerged. For some people this seemed to stem from a sense of being watched more closely, which prompted them to confront some of their lifestyle behaviours, or helped to reinforce good behaviour. This seemed particularly apparent for younger patients who were well-informed about their diabetes, and appeared to engage with the POC testing more than older patients.

Because diabetes can be invisible and often symptomless for a number of years, this could give rise to feeling of denial about the condition. For example, Sophie, 30, who had been living with diabetes for nearly three years and had uncontrolled levels of HbA_{1c} for a number of months, explained that if she avoided going for tests and getting an official result, it made it easy to ignore her diabetes.

"I was kind of deluding myself into thinking I'm on top of it; I'm in control, but I think it was obvious that if I were to go up there, check my blood sugar levels it would have been official that I'm not, so I just wanted to avoid that. ….I was eating really badly and I knew it was…it was really high and [um] I didn't test it very often because I knew the result and I didn't want to face it." [before POC testing]

During the second interview she reflected upon this behaviour. She felt that receiving the POC testing as part of the study motivated her because it was easier to see how her behaviour had made a difference compared with waiting weeks for results in standard testing.

"Yeah really helpful to [um]…to have [um]…have something to show that your behaviour is making a difference for you, helpful for you." [after POC testing]

With usual care, patients may not be able to see a clear link between their behaviour and the HbA_{1c} test result because of the time between the test and getting the result. Some patients could convince themselves that their behaviour had improved in the weeks between giving the blood sample and receiving the results of their HbA_{1c} test. Being confronted with a POC test result would mean that this is no longer possible.

"It's better…it's better for the patient because the information's there on the spot. They can't say, "Ah [um] that happened last week or, I've changed since the blood test"… It's there in front of them. There's, you know, rabbit in the headlamps, you've got them… The evidence is there so that's what I quite like about it because the evidence is there; there's no, "Well that was three weeks ago, I've changed" – that's what's your blood sugar level is there and then, that's your average, so let's address it." [P11, M, 55 years]

The face-to-face nature of the POC encounter facilitates a discussion of the result and can mean that it isn't as easy to ignore the result. Elaine, 50, who often forgets to take her tablets, said that she was encouraged to take her medications after getting her HbA_{1c} result in her POC appointment:

"[um] I was surprised. Yeah because I don't take the medication very well so I've been good this last week. Since I've had the appointment last week I've started taking my medication again and tried to be good…."

"And then I think it's very different having being told over the phone, "Oh yes your result is fine," or they want to come and discuss it. I think having it there in the, you know, in the surgery there and then is sort of, it's in your face isn't it?"

Frequency of testing

During interviews it emerged that not only the POC testing, but the frequency of the HbA_{1c} tests taking place in this study may have an impact of behaviour. The frequency of appointments, taking place at 3-month intervals during this study, was highlighted as an important facilitator in reinforcing good behaviour and reminding patients of their health status.

"Yeah and also going very often [um] and you are doing well, it reinforces the positive…the good behaviour you've been doing, and it encourages you to carry on…"

"I think one of the most important things is to be tested more often." [P50, F, 30 years]

The feeling of being watched more closely in the 3-month appointment really made some people think about their behaviour and compliance compared with even six-monthly monitoring intervals.

"Well I said to her I think, if you said six months I like to go perhaps mad or something on the three months or four months, and then you think, 'Ooh slow up down, really watch what you're doing,' because you've got your appointment in two months' time." [P73, F, 55 years]

Getting a bad result was shocking and disappointing for one patient who missed the middle study visit; she believed this was partly a consequence of having 6 months between appointments instead of the planned 3-monthly appointments in the study.

"Well to be honest it's not the end of the world and it's…and the reaction I had to the second…to the test was dramatic… I've got to change my life; I've got to do something. So, if that had happened midway I just would have had less to change." [P73, F, 55 years, after POC testing]

Immediate results and visibility

Overall, the immediacy of the POC test result evoked favourable responses. People talked about how the immediate result could reduce anxiety which arises from waiting for the result of the test during usual care. The instant result meant they could remember their recent eating and exercise patterns, and seeing the result in the surgery meant that there was no denying that the result was definitely theirs.

An immediate result enabled patients to link the result with their recent behaviour which could help them understand the impact of exercise and diet on their HbA_{1c} control. Sophie, 30, had been struggling to work out which foods she could eat, and which she should avoid. She found that having an instant result helped her to see how her recent eating habits affected her HbA_{1c}.

"[um] And [er] it's a great benefit to have the results straight away and then you can address all your concerns [er] in that appointment, within the same appointment. And [um] also based on the result you get you may have questions about [um] what did I do wrong; I've eaten too many fruits, and you can ask, "Is that OK, should I change the amount of fruit, or should I change the amount of bread and…," but if you get a result after several days and then you're having to wait another one or two weeks for the doctor's appointment, you may be…you can't remember everything you want to ask. So I think it's [um]…yeah it's a really good methods of doing things yeah." [after POC testing]

Anxiety about waiting for the HbA_{1c} result was highlighted as an important issue by several people, both before and after using POC testing. There was a general belief that POC testing would reduce the anxiety associated with feelings of uncertainty whilst waiting for their result. Sue, 49, had recently experienced some stressful episodes in her life, and felt that knowing about, and controlling, her diabetes was really important to her at the moment. Having to wait for her results caused her to worry.

"I think it would be, make a difference because when you wait for a week or whatever, you don't know what's wrong with you. You can't phone up and you're very anxious and

things, and that's what I am sometimes think … I hope my blood's alright." [before using POC testing]

After having the POC test Sue spoke about feeling more confident with knowing her result and getting immediate advice from the nurse.

"This is excellent because you'll know where you stand and then you can do something about it if your sugar levels up and down... And that's what I think, it's excellent, because sometimes when you wait for a letter through the post you think…or a doctor's going to ring you [um] and you think there's going to be some bad news. But there you can…[the nurse] can say, "Right I think you ought to go on these tablets to sort your sugar level out," than waiting for the doctor to tell you." [after using POC testing]

Graham, 75, also explained that he sometimes found it difficult waiting for his test result:

"I found it convenient; you know you're in there and it's…well not stressful's the right…not the wrong word, but the right word but having to wait two or three weeks before the doctor gets the note back, and then I might have to wait another week till I get an appointment time to go and see him." [after POC testing]

The uncertainty about how the result may affect future treatments was viewed as a source of anxiety; this could be a recurring experience for people whose diabetes is less well-controlled. Vanessa, 55, explained how one of her friends, who has been having discussions with the nurse about starting insulin over the past few months, gets perturbed waiting for the result every time she has a blood test.

"Yeah. It's the wait can also cause a lot of stress. I was just thinking my friend yesterday went in and had her blood tests. And she's texted me three times already saying, 'Oh I don't know if they're going to be alright; oh I'm really worried.' But she's the one that's on the cusp of taking insulin… So I think if she had her result immediately – yesterday, which is when she had her blood test – [um] and they could have discussed with her straight away and eased her onto the [er]…been discussing the insulin thing for months. Every time she goes in they sort of discuss it again, and so she's kind of got her head round it; she's ready to go and now she's got to wait and see and they might say, "No, actually it's fine so you're not going to go on it yet, but you will at some point," you know all this."

Visibility of the HbA_{1c} result with the POC test was deemed to be reassuring and reinforcing; however, some people felt that inclusion of trends would be valuable. Daniel

felt that although he may not remember his actual HbA_{1c} result, it would help him if he could see a graph showing where his target value should be.

"So, if healthcare management meant that I could kind of see my trends and see some graphs or charts of where some of the key metrics were going up and down, [er] I think that would help me personally in terms of, 'Ooh blimey right, you know I've been eating lots of doughnuts,' then that's what that's meant." [P74, M, 47 years, before POC testing]

Sophie, 30, a young woman who had struggled with denial, pointed out that getting an instant result from POC testing meant that there was no denying that the result was definitely hers:

"And you know what, I know… maybe, it sounds silly but it just crossed my mind at the moment – I know… well having your blood taken then and there… You know it's your result, and you know there have been mix ups [laughs], you know like…you know is that my baby, is that my blood? But you know I think it's really good, really good; I would…yeah I would have it this way, yeah definitely." [after POC testing]

Disadvantages and potential barriers to POC testing

Early on in the study there were some problems with cartridge failures and the nurse had to run multiple tests before the analyser gave a result. This was mentioned as a minor inconvenience to the patients involved.

"It was very good; I thought it was very good. The first time [the nurse] tried it, it was messing about a couple of times and…and it… It didn't work so we did it again and it did work… With persevering. She was pricking my finger about four times." [P02, F, 49 years, after POC testing]

Another theme which was explored was the perceived accuracy of the analysers. Bob, 73, said when he got his result he questioned the accuracy of the analyser because the result was different to usual.

"And that's the lowest I've ever been since I've had diabetes…. Which I was pleased and I thought afterwards, 'I wonder if that machine's right because it is a new one'" [after POC testing]

However, overall, patients felt confident with the analyser. Paul, 55, had recently given a blood sample prior to his first POC appointment and so was able to compare the results in the appointment and found they agreed.

"*Because I think the first meeting they took bloods and they did the point of contact [um] test as well and then they compared the result and they both said the same – blood sugars had gone up.*" [after POC testing]

Gita, 35, had expressed some concerns about accuracy during her first interview before having the POC test but after the test felt confident that the analyser was giving an accurate result

"Yeah because always is a first time, then we think is it…it's showing the right result; am I having the right treatment – you know that concern. So, how they do…do they do this blood test at the same time, like just to know how accurate it is? … But the thing is [um] just one test and is a new test, and it will show your result and my tablet dose will be changed according to that…. But anyway I'm not going to request it, it's just a concern." [before POC testing]

"So I thought that just with the finger prick how they would assess this last one, end of month things you know. It was just like it was a bit curious about that but now I trust it; now I trust the machine yeah." [after POC testing]

Sunita, 56, works in a care home where they use over the counter fingerprick devices for some of the residents. She felt that the POC HbA_{1c} analyser would be more accurate.

"Mm. Of that machine is it accurate? I mean the one that they use at work it's only a small machine so it's only giving you…but is it accurate, I don't know. But it's like any machine. Even if I bought a cheap one it will tell you that you are on high, but it wouldn't be like the proper machine." [before POC testing]

"I was confident yes. I suppose you know why, because I get…at work it's not proper; they just have these machines and, I mean you know those machines that you can get over the counter? … So, those aren't always accurate but I felt that this one was accurate yeah." [after POC testing]

One man, Simon, 57, who had type 2 diabetes but was treated with insulin couldn't see any advantages at all to POC testing. He usually only goes to the surgery to give a blood sample then gets his result over the phone without having to return to the surgery.

"I can't see a big benefit in getting it, you know instantaneously rather than a week later because that's generally what we get back, because it it's within a week." [before POC testing]

"Normally says yes, that's fine or …. The information that comes back is exactly the same, it's just swifter. What I'm saying is, it doesn't change the answer, it's just the speed of the answer… No all it's doing is getting the answer quicker. The system is working fine and personally they are happy with it and I'm happy with it… from a personal point of view I can see no advantage." [after POC testing]

Several people expressed concerns that POC testing may mean they did not receive their annual test in which other blood tests are performed. There was a general view that the annual test should be performed as usual, and POC testing should only be used for any HbA_{1c} monitoring in between.

"So if this is going to be my annual test; my only blood test of the year… Then there would be a concern that they weren't checking anything else especially as I get older." [P73, F, 55 years, before POC testing]

"The only question in my mind is that I can't remember whether it's every six month other things get…other blood tests get sent away… So, if that does happen… It might be pointless absolutely." [P74, M, 47 years, after POC testing]

Sylvia, 70, is insulin-treated and explained that she is usually only seen once a year by her GP for the annual test; for the visits in between she is managed in a clinic at the local hospital.

R: *"Normally I have to have a [um], a blood test – the [um] nurse takes the blood… And then it's sent off to Reading and then it's about four days later the results come back. [um] I still…I presume I'll still be having this [um] blood test which, because the [um] diabetic clinic in Reading I haven't heard whether they've got it for the main diabetic clinic which I go to every six months."*

I: *"Are you normally managed by your GP or by the clinic then in Reading?"*

R: *"Both… And usually my doctor has to have it done once a year [um] and results with the nurses and everything, and then I go to the diabetic clinic in Reading."*

5.3.4 Experiences of study participation and processes of care

Patients from each of the three surgeries felt that the clinicians liked using the POC device and spoke about this during interviews:

"I think…I spoke to [nurse] [er] at my last visit and she liked it… Because she's got more time I think because it's only [um] …it's not so rushed because it's only one visit every six months, as opposed to some have to come in, "Oh your bloods are slightly elevated, come back in three months."" [surgery 1]

"She thinks it's great" [surgery 2]

"Yeah, yeh he seemed quite chuffed." [surgery 3]

Five patients from one surgery (surgery 3) missed their second study visit. Reasons behind this and patient's feelings were explored during the second interview with the four patients who were part of the qualitative study. During the interviews it became apparent that the patients from surgery 3 were aware that they had missed one of their study visits. Vanessa, 55, speculated that the appointment was missed because the GP was too busy.

"I'm thinking about me missing that middle appointment. Maybe he just didn't have enough time to do it and that's fair enough."

Generally, patients who had missed the middle study visit were disappointed as they would have liked to have seen what happened to their HbA_{1c} between the 3 study visits.

"So, they missed the middle one which was [um] a bit disappointing for me, because I didn't feel like I was getting the full experience.… So, what's happened is that [um] they did the last one and my blood sugars had got worse." [P73, F, 55 years]

"No, I think that would be really interesting because I would…I would then have been able to have seen…I mean my understanding of HbA_{1c} is it kind of looks back at your last three months' worth of intake… If they were three months earlier that would have been interesting because we would have seen progress between the two or not." [P74, M, 47 years]

Daniel, 47, had recently had an appointment with the nurse just prior to his GP appointment.

"OK, so I'd been in for my regular check-up to see the nurse. I'd been in…let me have a think…perhaps two week prior to going in and having the session with the doctor and the machine… OK, so he was able to…on the system he was able to see the results that had come back as a consequence of my usual check-up… And therefore he knew that the result given by the machine corresponded pretty closely; I think it was within a small bit of difference to what the medical profession were saying my results meant."

Vanessa, 55, and Daniel, 47, clarified that their diabetes appointments were usually held with the nurse rather than the GP.

"I normally see the nurse; it was the doctor that was doing it this time."

"But you're right, it was led by…the practice doctor did the testing with me and had all of the meetings and all the correspondence was with him … But my regular diabetes check-up was with the nurse."

Patients suggested that the study appointments should have been with the nurse, because she usually carries out the diabetes appointments, knows their history, has access to all the educational materials and has more time for the appointments.

I: *"So it would have been better if it had been the nurse who'd done it?"*

R: *"I think probably … Probably because she knows my history."* [P73, F, 55 years]

"And if it transpires that the nurse is always doing the diabetes stuff then it probably should be in with the nurse." [P74, M, 47 years]

"If I'm honest [um] the nurse felt like she knew more I felt, perhaps unfairly, but my perception is my reality; I felt that the nurse was more of a specialist in this one particular field than the doctor was… it's more a feeling of the perhaps the compassion that the nurse had, the suggestions that she had, the fact she had leaflets and bits and bobs available to her to have that type of discussion. [um] It felt like, you know for her this is a main part of her job, because she does this probably twenty five times a week I'm guessing." [P74, M, 47 years]

"Oh she's wonderful. She will take as long as it takes, and she will discuss other issues which of course doctors don't do now. It has to be the ten minutes doesn't it you know." [P73, F, 55 years]

Vanessa had missed the second appointment and had been so concerned about her blood glucose levels that she had telephoned the nurse who had increased her medications a month before the POC appointment

"No, no it's always bad if it's gone up, it's always bad if it's gone up. Obviously being with the nurse, she's kind of more sympathetic and more likely to be kind you know. And she would more likely to say, "Look, it's not good news but we can deal with it," you know give you a bit of reassurance, whereas he kind of went, "Oh it's gone up, but you're seeing the nurse aren't you?"" [P73, F, 55 years]

Patients felt that because the analyser was in the GPs office, it would not have been possible for the nurse to use it; they felt that it would be best to locate the analyser in a communal space so all staff members can have access to it.

"So you really do need to be able to share it between the people who are dealing with diabetics" [P73, F, 55 years]

"It would make sense for it to be in the most used place… Yeah location where all medical staff can access it." [P74, M, 47 years]

5.3.5 Clinician attitudes to POC testing

The thematic framework used for basing coding and analysis of the clinician interviews is shown in Table 5.4.

Table 5.4 - Thematic framework for clinician interviews.

Theme	**codes**
Advantages of POC testing & Convenience	Not having to wait for result, liked analyser, better for people on changing medication, may be useful for unscheduled visits, convenience, useful for people who need frequent test
Clinical decision making and patient care	Feeding back result to patient, confidence at making treatment changes in the POC appointment
Practicalities and patient flow	Where would analyser be located, who would use the analyser, length of appointments
Disadvantages & barriers to POC testing	Annual review, costs, cartridge failures and storage, workload too big, accuracy

The clinicians had very positive views of POC HbA_{1c} testing. The perceived advantages included being able to monitor patients more closely and the potential for use in unscheduled visits. It was also recognised that POC testing was better for patients.

Even though there had been a few cartridge failures at the start of the study, clinicians felt that the analysers were easy to use and reliable.

"Yeah. So [um] I thought they were very good machines, I had no problems with them at all. I'd hardly ever had any [um] problems with the cartridge working or anything like that or…" [Surgery 2]

One nurse explained that it was better that patients did not have to wait for results which could cause anxiety in some people.

"they haven't had to wait that week, so for them…from them…for their point of view it's better because they're not sitting stewing, waiting for their results for a week or so beforehand." [Surgery 1]

Some clinicians felt that a big potential advantage of POC testing was having the opportunity to monitor patients more closely for a while if they have had a medication change.

"But sometimes when you do the annual bloods they're not OK. Everything's OK apart from the HbA_{1c} and then I'm often saying to them, "Make this change and do the HbA_{1c} again in three months," which is a whole appointment…. And then come back and see me, so it would take out an appointment and a lab test; you could just bring them back and do it here; that would be a…that's a huge advantage actually." [Surgery 2]

Another advantage viewed by one clinician was that it could be used for unscheduled visits or interim monitoring:

"Yeah, I mean I can see more how it would be with the sort of a more unscheduled visit. So, if someone goes to see [nurse] and maybe there have been issues with her insulin or maybe that's she's looking at [er] maybe changing their medication, and they come back and talk to her and maybe she'd do it there and then and see how…what progress they're making two or three months down the line you know, that sort of thing." [Surgery 3]

The effects of POC testing on the care pathway were also discussed, including length of appointments, best location for the analyser, and impact on patient care and clinical decision-making. Throughout the study, analysers were only used by a single operator at each site. Therefore they were located in the GP or nurse's office. It was felt that if the surgery was to adopt POC testing, then the analyser would need to be located centrally where multiple staff members would have access to it.

"Well we could have a centrally located one. I mean it doesn't have to…the only reason it's been in here is because I've been the only one doing it, but it's no reason why it can't be done in a centrally located area like in our middle room and then everybody has access to it [um] but then you have to go out of the room, I mean that might be a little bit more inconvenient." [Surgery 1]

"Yeah. [um] Yes probably more than one [operator] because… [the nurse]'s room is opposite, is the one who's most likely be doing it, so I suppose it could be in her room…. But in an ideal world it would be better if it's in a separate room that could be accessed by a number of people, and we've got, for example, between our treatment rooms down the bottom, we've got an area which is a utility area [er] where we keep the equipment, supplies etc and it would be fine in there." [Surgery 3]

Nurses observed that POC appointments were no longer than their usual diabetes appointments and that there was sufficient time to run the test, discuss the result and give necessary advice or changes to medication during the appointment.

"So, they were still here between about twenty and thirty minutes, so it actually wasn't, you know it didn't save time…It saved time overall because they didn't have their ten minute for their blood beforehand but actually the review time didn't change." [Surgery 1]

"But I didn't…I mean I allowed twenty minutes but certainly the follow-up visits they didn't really take that long, so while the test was doing we had a good chance to have a talk, and it wasn't…it was easily done in that time." [Surgery 2]

None of the clinicians thought that using POC HbA_{1c} testing would result in a change to patient care.

Interviewer: *"Do you think they'd changed the [um] patient care in any way?"*

Clinician: *"Not from our point of view really. Perhaps just offering a different way of approaching care that's all. I don't know from our point of view that it made us do anything particularly differently; we could just access results more instantly."* [Surgery 1]

The main potential barriers to POC HbA_{1c} testing were costs and concerns about missing the annual review. Some concerns were raised, and possible scenarios in which they felt that POC testing would not be helpful in patient care were suggested. Clinicians from each of the three surgeries all agreed that they wouldn't want use POC HbA_{1c} testing for patients' annual review:

"The only…the only downside that I could think is when they come for their annual review where they also need other blood tests, so for which we can't incorporate, so that might be a time when we don't use the machine." [Surgery 1]

"Well in some ways there might not be so much advantage of doing it in the annual test because you're doing it anyway." [Surgery 2]

"No, because you're going to take the blood anyway for their lipids and all the rest of it so a bit pointless really, it is expensive to do it that way." [Surgery 3]

Cartridge failures were experienced in two surgeries. One patient gave 3 finger-prick blood samples which all failed, so the nurse had eventually to take a venous blood sample.

"I think when the cartridges didn't work, and that was very annoying and annoying for the patients because they…one particular lady had got herself really geared up for, you know being able to use it and get her result straight away, and we couldn't get the cartridges to work and we didn't know why and…so that was…that wasn't so [um] positive an outcome. For us – frustrating for us and frustrating for the patient and having to explain and then having to get them, you know back again or, you know take a venous sample and then [um] get that result, so that was a bit of faff really so." [Surgery 1]

Cartridges can be stored long-term when refrigerated, but need to be allowed to reach room temperature before use which can take up to 15 minutes. One nurse mentioned that remembering to get cartridges out of the fridge was an inconvenience.

"I don't think…the only thing is you've got to remember to get it out the fridge." [Surgery 2]

Although it was recognised that POC HbA_{1c} testing was undeniably more convenient for patients, the GP did not think that it was more convenient for him, and thought that having someone else perform the test before the appointment may be better.

"It's not more convenient for us, for me… In a sense that it's much easier to get the [Healthcare Assistant] to take the blood, just have the result… Otherwise I actually have to set aside to actually physically do this… So, for me it's less convenient." [Surgery 3]

Currently GP surgeries do not directly pay for lab tests ordered, and therefore adoption of POC testing would be associated with costs to the surgery. This was raised as a concern, and would be a potential reason for not using these technologies:

"So it's probably broadly similar to the cost of the lab tests isn't it I would think? [um] The difference is of course we don't pay for lab tests directly. We're going to have a probably of…[um] pathology budget at some point; we don't actually formally have one yet but I'm sure that's coming. [um] So that would end up coming out of our overhead really… Ten thousand pounds a year and that could be an expensive overhead that we really wouldn't rather not have. So, I think that would be my main concern because obviously general practice is a small business and it could end up just costing us a lot of money and for something we could get done through the lab." [Surgery 3]

"If it's my decision on my own and [um] I was really making the decision, I still would say no because I know they'd say to me, "Why did you spend that money, it's ridiculous," but if it was [um] …if somebody said, "Well you can get…apply for some funding say from somewhere and you could get it," then I would decide to have it because I think it would be really useful… So if I felt that there was a way of doing that I could justify then…but I think I wouldn't be able to justify it at the moment because I know what the feelings are about [um] …because we provide quite an advanced level of diabetes here and I know the doctors feel that they're doing it unfunded … So they feel…they would feel to invest even more would…they wouldn't want to do that." [Surgery 2]

The missed second visits at Surgery 3 were explained by the GP. The timing of these appointments coincided with temporary unmanageable workload issues that were later resolved:

"Well it was absolutely fine except, as I said, the hiccup I had with the second visit; it was just because I was completely swamped. [er] Which was just a reflection of this place, nothing to do with [um] the study as such. It was just that I had two people off on maternity leave, people going off sick and we just had to cover everything, and I was just

working much more than I should have been working; I just couldn't really get round to do anything else."

5.3.6 **Rigour**

Several measures were taken during preparation, data collection, analysis, reporting and interpretation to ensure credibility of the findings (19). Patient and participant involvement groups were involved in the development of interview questions at an early stage in the project, and, after interviews had commenced, the ordering and wording of questions were adapted in discussion with two patient representatives. To ensure that the data collection and analysis process were robust, all coded transcripts, spreadsheets used to develop the coding framework and notes taken during the analysis were discussed with an experienced qualitative researcher and stored for future reference and transparency. Approximately equal numbers of participants were interviewed from each of the three GP surgeries to maximise the transferability and generalisability of results. Interview questions were worded as far as possible to be open questions to ensure that the responses were the opinions of the interviewee. The coding and charting process during the analysis were methodical and transparent to demonstrate a clear decision trail. Although the themes used in the analysis were predetermined and guided by a published framework (18), new themes emerged which were included in the synthesis because they were deemed to relate directly to the point-of-care testing intervention, though it is recognised that these decisions may have been influenced by the researcher. Quotes from verbatim text of patients' accounts were used when reporting results to support findings and allow the reader to make their own judgements on whether the themes relate to participants accounts. Summarising and interpreting the results have been compared with the peer-reviewed literature to maximise credibility. Results were presented to and discussed with two patient representatives and a General Practitioner. There may have been occasions when I may have influenced the data collection by making assumptions or asking leading

questions. Although the data analysis was based on themes informed by a framework (18), I may have approached the analysis with pre-conceived ideas; however, reporting of verbatim text in the results allows the reader to make their own judgements on this.

5.4 Discussion and conclusions

5.4.1 Summary of main study findings

This qualitative study has found that patients find POC testing convenient, and that it may help some people link their recent behaviour with their test result, thereby reinforcing good behaviours. The immediacy of the result reduced anxiety that some people experience waiting for their test result. Many people expressed some concerns that POC testing may mean that their annual diabetes review, in which multiple blood markers are measured, could be missed. Those who are treated with insulin have a different care pathway, which often involves management in hospital clinics, and there may not be as many advantages of POC testing for these people. Clinicians liked using the analyser and thought that it would not affect clinical decisions made, only the timing of decisions. Generally it was felt that POC testing should not be used for the annual review. Costs of implementing and delivering the POC tests were seen by clinicians to be the biggest barrier.

5.4.2 Strengths of this work

This qualitative study has explored patient and clinician views of POC HbA_{1c} testing to identify features of this intervention which may work best when implemented in UK primary care settings. It has revealed mechanisms by which POC testing may change patient behaviour and lead to improved outcomes. As well as identifying positive features of POC HbA_{1c} testing, it has also been possible to explore some of the reasons contributing to the incorrect delivery of the intervention, and to identify potential barriers

and scenarios in which POC testing may not work optimally. Each of these aspects can be used to improve how POC HbA_{1c} testing is implemented and delivered in future.

5.4.3 Limitations and generalisability of this research

This study was conducted in three GP practices in the Thames Valley where clinicians were all very motivated and provided a high level of care to their diabetes patients, which may not be representative of GP practices across the country. A maximum variation sample from patients was sought to get a breadth of perspectives, and this was largely achieved from the sampling framework, but it is recognised that the patients recruited to the study were likely to be highly selected and those who participate in research do not represent the general population. Although no conclusive statements can be made from this work, this study has revealed patients' perspectives and motivating factors which can be tested in a future study.

The sample of clinicians interviewed for the qualitative analysis of clinician attitudes was very small and from a selected group of GP practices. This may limit the generalisability of these findings.

Verbatim transcripts from each interview were checked for accuracy before analysis. However, another way in which rigour could have been improved could have been to ask the interviewees to review the transcripts from their interviews prior to the analysis and make changes accordingly.

5.4.4 Comparison with literature

In 2013 a systematic review of clinician attitudes to POC testing (20) reported that enhanced confidence, avoidance of missing or delayed results, enhanced communication and shared decision-making were amongst the facilitators to POC testing. Concerns about accuracy, undermining of clinical expertise, costs, equipment maintenance and time were

the major barriers to clinicians. This study has shown that the majority of these were not deemed to be barriers to adoption in three UK general practices. Only cost was viewed as a major hurdle, which is unlikely to be overcome without changes in current funding structures. This was also found in a recently published report on using C-reactive protein POC testing for detection of lower respiratory tract infection. The perceived barriers to adoption were costs and the need for suitable reimbursement models (21).

The only other qualitative study of POC HbA_{1c} testing carried out in UK GP practices (6) found that, in general, patients were satisfied with their usual care, and extra surgery visits were not generally seen as a problem. Nurses reported advantages in terms of having the result available for discussion with the patient and saw this as beneficial for patient education. In that study, randomisation took place at a patient level within each GP practice, and the authors acknowledged that as a consequence the practices found it difficult to "*organise their management of patients with diabetes in such a way as to maximise the benefits of using the rapid test for intervention group patients. Practices therefore often continued their follow-up in the usual way*" and that "*the patients in many instances continued to attend twice*". The qualitative findings from the study may not therefore have been able to accurately reflect patient views of a point-of-care testing consultation in which action was taken on the result (8); moreover the convenience of receiving this type of testing would be negated for those patients who still attended the surgery twice. The work presented in this thesis is therefore the first in the UK to explore patient and clinician perceptions of POC HbA_{1c} testing when implemented correctly.

Findings from this work have highlighted the importance of regular and frequent monitoring for some people. Regular monitoring can help them to remain motivated and to reinforce behaviours or aspects of their lifestyle which help their diabetes control. This may be linked to the asymptomatic nature of diabetes in which a deterioration in HbA_{1c} is

invisible to the patient and can be easily ignored. Monitoring indicators of health status can both give the patient the sense of 'being watched', but also provide the patient with reinforcement of good behaviour which may encourage them to continue. There have been similar findings with telemonitoring of blood glucose and blood pressure in diabetes (22), where patients considered the 'policing' aspect of telemonitoring important in managing their condition. Hypertensive people who self-monitored their blood pressure similarly recognised the importance of regular monitoring because of the silent nature of hypertension and severe consequences of high blood pressure (23). More frequent monitoring has been shown to improve outcomes in other conditions; measuring weight on a daily basis resulted in greater weight loss than weighing less often through enhancing self-regulation (24). Moreover, frequent monitoring in combination with visual feedback on progress may also improve motivation through reinforcement of behaviour (25). It is however, pertinent that these monitoring processes are based on objective outcomes which are not subject to interpretation.

Interestingly, it is unlikely that monitoring alone is the motivator for behaviour change: providing pedometers to participants to increase activity levels found no significant change in activity levels; only when a pedometer was provided in combination with a daily step goal did activity levels increase significantly (26). Patients who are aware of their target HbA_{1c} value tend to have better glycaemic control than those that do not know their target (14). There is growing evidence that patients who are actively involved in their healthcare have better health outcomes and treatment satisfaction (12, 13). Patient motivation to take an active role in managing their condition through involvement in decisions about their care, treatments and lifestyle choices could be facilitated by POC testing (11). This is an important consideration for future studies. Motivation to be informed about health status and playing an active role in care is more common amongst

younger people, with older age, male sex and lower education being predictive of playing a passive role in healthcare (27). This suggests that POC technologies may be particularly helpful in engaging younger people in their condition.

This work has revealed that some patients found the visibility of the POC result helpful and reassuring. Diabetes control has been found to improve when patients are given a graphic record of trends in their HbA_{1c} over time (28). Some GPs already offer visual feedback of HbA_{1c} to their patients by allowing them to look at the computer screen with the result as well as the trends in their glycaemic control. Other research has found that giving the patient a health passport which is a patient held record of glycaemic control and feedback from appointments leads to small improvements in HbA_{1c} (29).

Reducing anxiety which stems from waiting for test results was viewed to be an important benefit of getting an immediate result with POC testing by patients in this study. Reduction of anxiety with immediate results has previously been reported: ninety-seven percent of women who were surveyed about mammography screening reported that having an immediate result would reduce anxiety (30). However, a rapid test for prostate specific antigen did not reduce anxiety in patients getting immediate results compared to those who had a lab test and received the results 1-4 days later (31). Monitoring of oral anticoagulation therapy, as for HbA_{1c}, can involve a INR laboratory test, or rapid testing; a randomised trial comparing self-testing with laboratory testing found the usual care group had higher anxiety scores than the telemedicine group (32).

5.4.5 Relationship of findings to framework

In Chapter 4, a theoretical framework was proposed on how POC HbA_{1c} testing could be correctly delivered and measured by quantitative and qualitative outcomes. The quantitative outcomes were presented in Chapter 4 and the present Chapter has reported

results from the qualitative interviews. The findings from this Chapter confirm that most aspects of POC testing were delivered correctly and that the streamlined care pathway was more convenient and preferable to most patients. It has also raised the possibility that the clinician delivering the care and the workload in the surgery may be factors which could influence the correct delivery of the intervention, but this would need to be confirmed in a future study. Cost of delivering this intervention was the only pre-specified barrier which was confirmed in the qualitative study.

5.4.6 Implications for clinical practice

This work has highlighted several important features of POC testing which may encourage behaviour change and adherence. The reinforcing nature of POC testing was a salient factor. This was closely linked with more frequent testing, and may re-engage some patients who may have had a tendency to slip into non-adherence. The immediacy of the result helped patients link their recent behaviour over the past few weeks with their HbA_{1c} test result. Therefore regular and frequent appointments may help to reinforce and motivate some patients, as may goal-setting and use of visual aids to monitor trends. Patients who were insulin-treated only saw the GP for their annual review and were otherwise managed in hospital clinics. Moreover, this group usually monitor their blood glucose levels. POC testing for these patients may therefore have fewer immediate advantages.

The main barrier to POC testing was cost, which was highlighted by clinicians as a concern. There was also an overall perception by patients and clinicians that POC testing should not be used in place of the annual diabetes review in which several other markers of health status are measured.

5.4.7 Implications for this research

It transpired from qualitative interviews that patients felt their POC appointments should be conducted by the clinician who usually provides their diabetes care, and that nurse appointments may be better than GP appointments. This may be particularly pertinent in very busy GP practices where GPs may feel the pressures of high workloads more than nursing staff and are under pressure to keep appointment times short (33).

5.4.8 Conclusions

This work has highlighted the preference for POC HbA_{1c} testing by patients and suggested mechanisms by which it may lead to behaviour change. Whether these lead to actual behaviour change and improvement in outcomes is not yet known. This work has also identified some of the major barriers to POC testing which would need to be carefully considered both when designing a future study, but also for surgeries considering implementing these technologies. The next chapter summarises the findings from this whole thesis and proposes an outline design for follow-on work informed by this thesis.

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6.1 Introduction

In this chapter I will draw together the four different aspects of my thesis to present the key findings and discuss how these compare with previously published work. I will summarise the conclusions, the implications for clinical care, and identify areas which still need further research. I will use the findings from this research to outline proposed future studies to optimise and test how point-of-care (POC) HbA_{1c} testing can be used in UK primary care.

6.2 Overview of this research

This thesis builds on the knowledge of how HbA_{1c} is tested in the UK, and has explored how POC HbA_{1c} testing may be used in primary care consultations. This research has reported current practice in HbA_{1c} testing, summarised the accuracy of POC HbA_{1c} test devices, and investigated how POC HbA_{1c} testing could be introduced into a routine diabetes consultation in primary care settings. This was achieved by collecting data on the appointment process, care pathways, technical feasibility and patient and clinician behaviour following published frameworks (1, 2). To achieve this, four pieces of research were carried out, which comprised of: describing and analysing current practice and behaviour in HbA_{1c} testing in primary care, a systematic review and meta-analysis of POC device accuracy, a feasibility study to examine POC test delivery and implementation, and qualitative work to understand its acceptability and the effect on behaviour. Findings from the first three chapters of the thesis (which include the review of the literature in Chapter 1) were used to inform the design of the feasibility study. Results from the feasibility study have demonstrated that POC HbA_{1c} testing can be physically delivered and fed back to patients within a primary care consultation, but whether the results are acted on in the consultation may vary between settings. Likely rates of recruitment, follow-up, technical failures and limitations with instrument accuracy were determined, and contexts and

patient groups in which POC testing may be most likely and less likely to be successfully implemented have been suggested. Likely mechanisms by which POC testing may lead to patient behaviour change were also explored to attempt to explain how POC testing could improve patient outcomes.

6.3 Key findings

The findings from each of the individual chapters are summarised as follows:

Chapter 2 - Description of patterns in HbA_{1c} testing

- Over- or under-frequent HbA_{1c} testing is more common in patients with high HbA_{1c} and in the four months immediately prior to the QOF deadline on 31st March than at other times of year
- Over- or under-frequent HbA_{1c} testing in primary care is associated with GP practice-level factors and GP incentive schemes.

Chapter 3 - Accuracy of POC HbA_{1c} test devices

- Most POC HbA_{1c} devices have a mean negative bias compared to laboratory methods.
- Devices tend to have high sensitivity rather than consistently high specificity.
- There is large and unexplained variability in measurements within and between devices.

Chapter 4 - Feasibility study of POC HbA_{1c} testing

- Nurse-led POC consultations successfully recruited and followed-up 24 patients.
- Appointment times were no longer than usual care.
- Clinical decisions were made using the POC test result in 58% of consultations.

- GP-led appointments in 5 patients were shorter than nurse-led consultations.
- GP appointments did not replace, but ran alongside usual diabetes care appointments.

Chapter 5 - Qualitative interviews with patients and clinicians

- Overall there was a very positive attitude to POC testing, which, in general patients reported to be more convenient compared with their usual care.
- The immediate result reduced anxiety waiting for the result and helped some people to link their HbA_{1c} result to their recent behaviour.
- Some people felt that having more frequent tests and getting the result in the appointment forced them to confront their diabetes and related behaviours.
- Healthcare professionals found the tests easy to use but thought that cost issues would be the major barrier to whether they are used in future.

6.4 Findings from this work presented in the context of a framework

Findings from this thesis have been presented in the context of a framework for the evaluations of diagnostic tests (2) in Table 6.1.

In brief, the feasibility study has demonstrated that delivery of the test successfully took place in all but one of the scheduled patient consultations. There were some technical problems due to cartridge failures, but each of these could be explained and could be rectified through more careful training of laboratory and clinical staff. Clinicians found the test result to be easy to interpret, and the accuracy of the analyser was not viewed to be a concern by patients or clinicians. The result was fed back to the patient for each successful test, and treatment decisions were made during the consultation in the majority of appointments, though this may be clinician-dependent. All clinicians reported that they felt confident about making treatment decisions in the POC appointment. Depending on

the timings of follow-on appointments in different practices, treatment changes could be received one to three weeks earlier than would have taken place in usual care, though in some cases the wait for a follow-on appointment in usual care could be longer than this. Results from qualitative interviews suggested that POC testing may encourage medication adherence in some patients.

Table 6.1 - Results within a framework for evaluating diagnostic tests.

	Attribute of test-treatment pathway	**Effect of POC testing**
Diagnostic test delivered	Timing of test	Time to results was 3 minutes. Test was easily delivered in nurse consultations (average consultation time: 23.8 minutes). Test during GP consultations (11.4 minutes) was not felt to be a good use of GP time.
	Feasibility	Test was successfully completed in 52 out of 53 POC consultations (98%). There were a total of 11 cartridge failures in six patient appointments.
	Test Process	Patients liked receiving the test and most found it more convenient to their usual testing process.
Test result produced	Interpretability	Clinicians believed the test result was easy to use and interpret.
	Accuracy	Between-patient variability found in results from POC analyser may have led to some differences in treatment decisions.
	Timing of results	Results were received during the appointments and were viewed to be preferable to patients and clinicians.
Diagnosis made	Timing of diagnosis	Test result received within the consultation.
	Diagnostic yield	Treatment change or advice made in 30 out of 52 consultations (58%).
	Diagnostic confidence	Clinicians all felt confident in interpreting and acting on the result within the consultations.
Management decided	Therapeutic yield	Effect of new test on treatment decisions could not be measured in study design.
	Therapeutic confidence	Clinicians felt confident with making treatment decisions based on the test result.
Treatment implemented	Timing of treatment	Treatment changes take place 1-3 weeks sooner with new test depending on how quickly results received and follow-on appointment can be booked.
	Treatment efficacy	The effect on patient outcomes could not be measured in study design.
	Adherence	There was no evidence that POC testing improved adherence from questionnaire scores. Qualitative interviews suggested that some patients may be encouraged to take their medications.

Two parts of the framework could not be addressed using the study design and remain unanswered. These are: what impact POC testing had on treatment decisions, and patient outcomes compared with the usual testing process (highlighted in grey in Table 6.1).

6.4.1 How might POC testing change behaviour?

An important aspect of a new intervention is the impact it may have on behaviour change (1, 2). Results from qualitative interviews have been reported in detail in Chapter 5 along with some key themes which emerged on how POC HbA_{1c} testing may lead to patient behaviour change. These themes: being more closely watched, reinforcement of good behaviour and visibility of result, are discussed below.

There was a perception by some people that they felt they were being watched more closely during POC testing. This may encourage some people to think about how their lifestyle behaviours may be affecting their HbA_{1c}, particularly in the weeks coming up to an appointment. During the study, patients received three-monthly HbA_{1c} testing, which was more frequent than the majority of patients would usually receive. It is possible that this more frequent testing contributed to feelings of being more closely watched by healthcare professionals. How more frequent testing impacts on patient care and health outcomes needs to be separately explored.

Receiving the HbA_{1c} result in the appointment helped some people to understand how their recent behaviour could impact on their HbA_{1c} test result, because they were able to remember their exercise or eating patterns over the previous few days. People are less likely to accurately recall behaviours from when their blood was taken 2-3 weeks earlier in usual care appointments. On this basis, POC testing may help people to more easily link their lifestyle behaviours with their test result. If the POC HbA_{1c} result is lower, this may reinforce good behaviours and potentially encourage them to persevere.

Most people with type 2 diabetes who are not taking insulin do not self-monitor blood glucose levels; therefore the only monitoring of glycaemic control which these people receive is their HbA_{1c} test. A POC test result may provide a more visible indicator of diabetes status than is provided by laboratory testing because the result is displayed on the analyser screen during the appointment. Moreover, the result represents their current glycaemic status, which may be more difficult for some people to ignore.

These all provide likely mechanisms which may lead to behaviour change. Nevertheless, patients' overall perception of POC HbA_{1c} testing will be crucial in determining how well this intervention works in practice because of the effect on adherence to medication and appointments and other downstream health behaviours (2). In qualitative interviews, the majority of patients expressed a preference for this type of testing. This favourable perception of POC testing, and possible influence on patient behaviour may be a more important factor in determining whether POC testing ultimately improves health outcomes than the more rapid time to test result and treatment changes which POC testing offers.

6.5 Strengths and limitations

This work presents a structured approach to evaluating the use of POC HbA_{1c} testing in UK primary care consultations through following guidance and frameworks (1, 2). Patterns in clinician HbA_{1c} testing behaviour found in the John Radcliffe Hospital laboratory data which may influence the appropriate use of POC HbA_{1c} technologies were confirmed in CPRD data. The systematic review of POC HbA_{1c} devices is the largest and most comprehensive analysis to examine how these technologies may perform in everyday practice. The results from this helped to make an informed choice in selecting a device considered to be the most acceptable and suitable for use in the feasibility study. Use of a mixed methods design has helped to ascertain how POC testing could lead to behaviour change, as well as providing explanations for deviations from the protocol which took

place during the feasibility study. These important findings may not have been brought to light if only quantitative methods had been used, and illustrate the value of including a qualitative element in this research as advocated in the MRC guidance (1). Use of qualitative methods has also made it possible to identify scenarios when POC testing may be less useful, or lead to poorer care; these still need to be studied in greater depth in a future study.

There are however, a number of limitations to this work which are presented in detail in the separate results chapters. Although the hospital and CPRD analysis suggest that GP HbA_{1c} testing may be influenced by the QOF deadline, this is only an association and causation cannot be inferred from this data. Moreover, there are inherent problems with using this type of data, for example, some people may be moving in and out of the dataset. Some patients included in the dataset may have comorbid conditions that were not analysed which may have meant that monitoring within guidelines was not feasible or appropriate. No indicators of social deprivation were included in the models, which may have been associated with GP or patient-level differences in testing patterns.

There were few evaluations identified for the systematic review which had been carried out in a clinical setting. According to Larsson *et al.* (3), "a pre-requisite for obtaining benefits from a POC test is that the test is sufficient for medical decision-making in the clinical setting." Because the majority of devices did not have any evaluations in a clinical setting, the performance of these devices in a real-life setting could not be compared with the more common laboratory-based evaluations.

The feasibility study was not powered to detect any quantitative outcomes, and the questionnaires or quantitative measures were not found to change with POC testing. Patients in the study were already satisfied with their care and engaged with their diabetes

at baseline which may have limited the potential to measure any further benefit using the questionnaires. This may have been a reflection of the patients recruited to this study who were from a selected population. The qualitative interviews instead provided a better indication of likely effect on behaviour of patients, which demonstrates a strength of the methodology used in this work.

It is recognised that this study has only recruited GP practices with highly motivated staff with a specific interest in the subject area which may not be typical, particularly when compared to practices in more deprived parts of the country (4). This may have led to the recruitment of a highly selected group of patients to the study. Understanding the importance of both context and patient deprivation and how these affect delivery of the intervention should be something that a future study explores.

Although I set out in this project to identify how POC HbA_{1c} testing could best be implemented into primary care consultations, the findings from this work are by no means exhaustive. It is recognised that there are likely to be many circumstances where these technologies may not be optimally applied which may emerge in future work. This work, however, has been effective in understanding some of the scenarios which may be a barrier to implementing this type of testing which could be explored in a future study.

6.6 Relation to the literature

This work has found that HbA_{1c} testing behaviour may be influenced by QOF incentives; the introduction of QOF in 2004 reportedly led to an improvement in overall quality of care, including the appropriate monitoring of people with diabetes (5). The analysis reported in this thesis only included follow-up in a cohort of people from 2005 to 2014 after the introduction of QOF; it was therefore not possible to compare findings with testing behaviour before the introduction of QOF. Increased rates of testing outside

guidelines in the months preceding the QOF assessment date are most probably attempts by GPs to ensure that i) more patients meet target HbA_{1c} ranges, and ii) patients receive their annual review. Both of these would culminate in greater financial rewards for GP practices through QOF reimbursement. According to the Health and Social Care Information Centre, "*QOF rewards practices for the provision of quality care and helps standardise improvement in the delivery of primary medical services*" (6). Whether meeting QOF targets is also associated with improved patient health and long-term outcomes is not addressed by this research, but other reports suggest that the introduction of QOF has not reduced ethnic disparities (7) or improved long-term health outcomes (8).

Results from the feasibility study have demonstrated that carrying out a POC test and acting on the result during the consultation may sometimes be challenging for GPs, particularly when workloads are high and GPs are overstretched. During the study, it materialised that staffing problems and a quality inspection, which took place whilst the study was on-going, were major factors contributing to protocol deviations. GP practices in the UK are inherently overstretched, with many GPs juggling too many patients and unrealistic workloads (9). Successfully implementing a new intervention in an environment with competing demands is contingent on health professionals adopting the intervention and abandoning old practices. However this may be particularly difficult in over-constrained systems (10). Resistance to adoption of new testing processes where primary care providers had logistical challenges and workload demands has been observed previously (11). Overcoming inertia to encourage the adoption and correct use of a new intervention may, in some cases, only take place if incentives are offered (10).

Concerns about remuneration were found to be the major barrier to the adoption POC HbA_{1c} testing raised by clinicians in the qualitative interviews. This has been seen in other disease areas where reluctance to take up different types of testing was attributed in part to

worries that there will be no mechanism for financial compensation (11). Unless POC HbA_{1c} testing is found to have a clinical benefit, or a cost-effectiveness analysis demonstrates overall financial savings, changes in funding structure and incentive schemes are unlikely to take place, meaning that costs may remain a permanent barrier to adopting these technologies in the UK. POC C-reactive protein (CRP) testing is advocated by recent NICE guidelines for people presenting at their GP surgery with symptoms of lower respiratory tract infection (12). Estimated costs of CRP POC testing would involve an initial investment for purchasing analysers, and thereafter costs of £13.50 per test (12); it is suggested that cost savings from POC CRP testing would arise from reduced antibiotic prescriptions and more timely diagnoses resulting in reduction in hospital length of stay.

A recent report has proposed models for financing CRP POC testing in primary care (13) which range from direct purchase by the primary care practice or clinical commissioning group to leasing from central laboratory services or direct from industry. The latter options may be preferable for GP practices because training, maintenance and quality control could be included in the agreement. Procurement of POC HbA_{1c} testing by primary care could fit into a similar structure, though it is still unlikely that adoption would take place without clear mechanisms for reimbursement. The cost of an HbA_{1c} test was estimated by NICE to be £4.04 in 2011 (14). In a recent personal communication with laboratory staff at the John Radcliffe hospital in Oxford the hospital charges GP practices between £5.50 and £6 per HbA_{1c} test. These costs are only for the laboratory analysis and do not include phlebotomy and transport. A cost of £6.30 per test has been estimated by the John Radcliffe hospital to provide a full POC service to GP practices including the supply of cartridges, training and quality control. This would not include the initial purchase or loan of the POC analyser which would increase the overall costs. Nevertheless, these estimates

suggest that cost of performing a POC test appears competitive with lab analysis. Furthermore, this model provides the lab with control over the technology used, connectivity to ensure that patient health records are automatically updated and quality control, as well as maintaining a source of revenue for the lab (3). Before the real costs of POC testing to the health system and patient care can be understood, a full health-economic analysis needs to take place.

This thesis has identified that HbA_{1c} testing within nurse consultations may work better than GP consultations if POC testing is to be adopted in primary care. A previous study also found that clinicians find it difficult to change usual practice in a POC consultation (15). Interestingly, nurse-based consultations have been associated with more appropriate intensification of medications in primary care consultations in The Netherlands (16). A recent systematic review found that a combination of nurse and GP care resulted in lower blood pressure and cholesterol in people with type 2 diabetes, compared with GP care alone (17). An Irish study reported that GP practices without a practice nurse found administration of a new screening programme for gestational diabetes particularly difficult (11). Full explanations for these apparent benefits of nurse-based care for some conditions are not given in the reports, but the longer consultation times with nurse appointments may be a contributing factor.

6.7 Lessons that have been learnt

During the feasibility study it transpired that, despite instructions to clinicians to base clinical decisions and medication changes on the POC results, this did not always happen. This may have been because consultations in one surgery were handled by the GP rather than the diabetic nurse, who would have usually been the clinician carrying out the routine diabetes appointments. Moreover, because of high workloads, patients in that surgery were not invited for their second study visit, which meant they only had one POC test during

their study participation. Prior to their final study visit, some patients had recently had a routine diabetes appointment with the practice nurse; in some cases this had included an adjustment to their medication. This meant that a further adjustment to medication in the POC appointment may not have been appropriate despite high POC HbA_{1c} results. A future study may be more likely to proceed according to protocol if the POC appointments are held with the clinician who usually provides diabetes care. Although there is no guarantee that this in itself would result in the test always being correctly delivered, findings from the qualitative interviews suggest that clinicians liked using the test and did not find it difficult to use the results to base their clinical decisions. There was therefore no indication by the usual care providers that this would be a barrier to them.

This work has revealed that there are some circumstances when POC testing may be less beneficial:

i. *Annual review*

   In patient's annual diabetes review, patients provide a blood sample which is tested for multiple markers indicative of health status. Because a venous blood sample is taken during this review, there may be little benefit to performing a separate POC HbA_{1c} test unless there is particular concern about the patient's glycaemic control. There was a general concern by patients and clinicians that the introduction of POC HbA_{1c} testing in their practice may result in the annual review sometimes being missed.

ii. *Insulin-treated patients*

   People treated with insulin often test their own blood glucose levels on a daily basis and adjust their insulin doses accordingly. Management for these patients often takes place in hospital-based clinics and they may only be seen by their GP for their annual diabetes review. POC testing in a primary care setting may

therefore be less useful for this patient group. Many previous studies of POC testing did not exclude or separately analyse data from people who were insulin-users (18-20) which may have contributed to the lack of effect of POC testing on HbA_{1c} found in these trials (21). Although it is still not clear whether POC testing is inherently unlikely to make a difference to glycaemic control in these patients, the management and care of insulin-treated diabetes differs sufficiently from those who are diet-controlled or taking glucose-lowering medications to suggest that they are less likely to benefit from POC HbA_{1c} testing in a primary care setting in the UK. Hospital-based clinics, on the other hand, often use POC HbA_{1c} testing, particularly for paediatric patients.

POC testing may be most beneficial for close monitoring of patients who have less well-controlled diabetes. This would minimise inconveniences to patients who may be receiving more frequent tests, and allow clinicians to quickly test HbA_{1c} in diabetes patients who are not regular attenders and present at the GP surgery for other reasons.

This thesis has illustrated that POC HbA_{1c} testing can be implemented in primary care consultations. It is now important to ensure that each of the factors identified to contribute to the successful implementation is fine-tuned to form an integral part of the intervention which can then be delivered in future studies. In this research, questionnaires did not capture the full range of opinions about POC testing which became apparent only after qualitative interviews. In hindsight, this may have in part been a result of using the same questionnaire at the start and end of the study. Designing an end-of-study questionnaire which specifically focussed on differences between usual care and POC appointments may be more suitable for picking up preferences in a future study.

6.8 Clinical implications

There is currently an enormous amount of pressure on GP practices in terms of clinical workload and funding (22). The integration of a new technology into a GP consultation would therefore have to be perceived as having benefits in terms of reducing overall workload or appointment times, as anything which prolongs the patient consultation is likely to be viewed negatively. POC testing expedites the turnaround time in testing, but it remains unclear on whether this ultimately has an effect on the clinical decision-making process, workflow, and patient outcomes (3).

As well as demonstrating how POC testing may change diabetes appointments and care, this work is unique in providing a detailed overview of the range of POC devices and their performance. It provides evidence that full connectivity and synchronising results with patient records can be achieved in everyday use. This connectivity could be critical in minimising human error if POC testing is to be implemented (23). This work will aid clinicians who are considering using POC HbA1c testing to make an informed choice based on the performance and features of analysers to decide which best suits their clinical needs. Despite this, the impact of accuracy and variability observed in these devices on clinical decision making and patient outcomes is still not known (3). These still need to be tested in a randomised trial.

The research in this thesis has found that GPs' HbA_{1c} testing behaviour may be influenced by financial incentives. QOF has been shown to improve monitoring in primary care (5, 24); for those with diabetes, this has ensured that the majority of people are seen at least annually by their GP or practice nurse. Because of over-constraints in the NHS, and GPs in particular (9), making changes or adoption of new technologies, even those which may result in time-saving, cost-saving or overall patient benefit, may not take place without introducing incentives (10).

This suggests that motivating widespread adoption of a new technology in primary care in the UK may require a combination of a change in guidelines and reimbursement. Encouraging GPs to adopt POC testing may require a series of steps which could include i) changes in funding structures to make it easier to pay for machines and run tests, ii) incentives to encourage this type of testing and iii) costs of technologies to come down as markets open up and competition increases. Introduction of funding structure change would need to be anchored on proven benefits to patient outcomes.

As discussed in chapter 1 of this thesis, the NHS five-year forward view (25) points out that better integration between different aspects of care is needed. These changing models of care may mean that insulin-users, who currently receive much of their care in hospital-based clinics, receive more of their diabetes management in primary care. This could be helped by new technologies such as POC testing, which change the traditional models of diagnosis and monitoring. As well as testing in GP practices, POC HbA_{1c} testing could be delivered by pharmacies, which may be preferred by some patients due to their relatively wide accessibility. HbA_{1c} testing in pharmacies has already been piloted in Canada, where pharmacists have clinic days when POC HbA_{1c} testing is offered and medication, lifestyle and health history are reviewed (26). Because of their portable nature, POC technologies also offer opportunities for mobile clinics or testing in nursing homes where patient mobility is restricted. Over time, the costs of this type of testing will decrease as technologies develop and competition increases, which may open up other opportunities for testing in community settings.

6.9 Implications of this research and future work

In 1999, it was highlighted that there was insufficient evidence to support POC HbA_{1c} testing in UK primary care (27, 28), and in 2010 this view was re-iterated in an editorial (29). Yet, further evidence verifying whether POC testing has the potential to improve

care has still not been provided. Nevertheless, the National Academy of Clinical Biochemistry in the United States recommends the use of POC HbA_{1c} testing for monitoring in diabetes (30).

This thesis has improved the understanding of how POC HbA_{1c} testing could work in practice by examining the impact of the test on aspects of the test-treatment pathway. It has demonstrated that a new clinical pathway using POC HbA_{1c} testing in primary care settings can operate as intended, but this pathway may need to differ between settings. It has also identified likely mechanisms by which POC testing may lead to behaviour change or where problems may arise. This is valuable preparatory work for future studies in this area to test the downstream effects of the test on patient outcomes.

What this work has not been able to establish is whether additional problems arise in urban areas or areas with high levels of social deprivation. It has also demonstrated that even in motivated GP practices in affluent areas of the UK, there were problems with recruitment and follow-up of patients. Future studies may need to consider whether the provision of incentives or forms of reimbursement are needed to ensure that research activities can be carried out in addition to clinical duties.

It is still not known whether POC testing, even when implemented correctly, will ultimately lead to changes in treatment decisions, patient behaviour and longer-term health outcomes. POC testing is likely to offer the most benefit if it is to be part of a wider package of care which could include patient education. This may mean that training or education packages delivered to clinicians and patients would need to be offered as part of the POC package.

Measurement of longer-term outcomes from POC testing could be tested in a randomised trial. If long-term follow-up is not possible then changes in HbA_{1c} could be used to model

other health outcomes. Data linkage could be used to follow-up morbidity, mortality and longer-term clinical outcomes. Collection of health economic data in a future study would be needed to compare the cost-effectiveness of POC HbA_{1c} testing with usual care. However, before this can take place, there are still some aspects which are not well understood and require further investigation. These are summarised below.

6.9.1 What is still not known?

Randomisation

A trial published in 2006 (15) randomised patients to POC testing or usual care at the patient level within practices. Clinicians from surgeries taking part in the trial found it difficult to change current practice in those patients who were randomised to POC testing. They continued to schedule a second patient appointment to act on results and adjust medications if necessary. The alternative to randomising at the patient level is to randomise practices to the intervention or to usual care; this would require a larger trial to measure differences in effect sizes because of the clustering effect (31) which would incur extra costs. Cluster randomisation would eliminate the possibility of cross-contamination arising from those who are randomised to usual care receiving a POC test. A caveat of cluster randomisation is that it would make it difficult to make comparisons between practices which offer different models of care, or between those which have different patient demographics. Although it may be preferable to use cluster randomisation in a definitive study of POC testing, randomising at the patient level in a pilot study may be a pragmatic option to make it possible to explore the differences between GP practices.

Funding structures and costs

To overcome the potential financial barrier to POC HbA_{1c} testing, there may need to be some level of reimbursement or incentive to encourage adoption. This could involve direct purchase by the GP practice or a loan from either the NHS, hospital laboratory or direct from industry. A loan agreement would have some advantages over direct purchase as it could include a contract to cover QC, maintenance and training (13). Whether this model works in practice, and costs of delivering the intervention are important to consider and should be measured in a future study to allow comparisons with usual care.

Nurse versus GP consultations

It remains unclear whether POC testing is more likely to result in changes in care with nurse-led consultations compared with GP-led consultations. A model in which the GP runs the test is likely to be time-pressured as appointment durations are already so short. Therefore a comparison between nurse-led appointments (with prescribing capabilities) and a POC test operated by a healthcare assistant followed by GP appointment, could be explored.

Frequency of testing

The single appointment in POC testing would make it easier to more closely monitor HbA_{1c} in those patients who need it. In some cases this may include more frequent visits, but it is important that effects from POC testing and more frequent HbA_{1c} tests are disentangled. Designing a study which allows these to be individually explored would be necessary to allow any benefit to be construed from POC testing.

Contextual factors

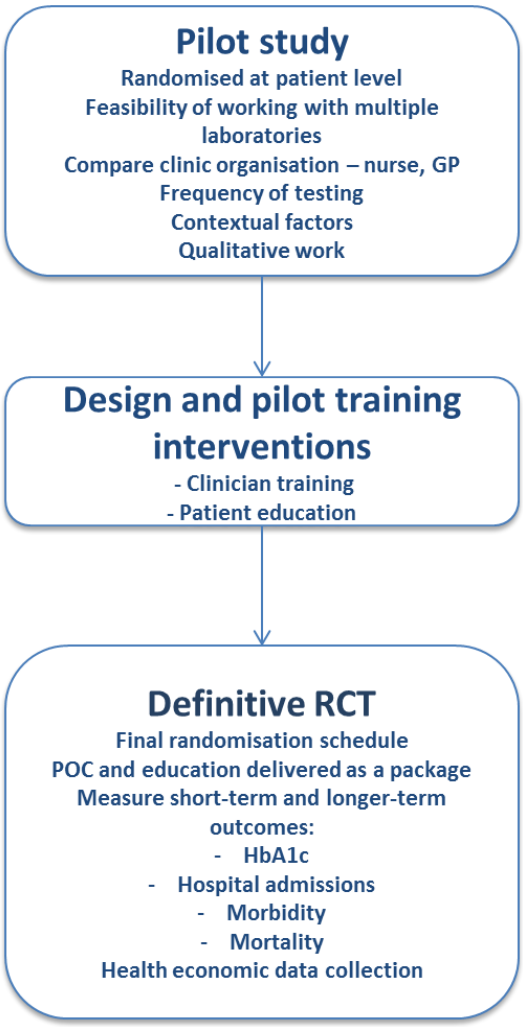
The context of the GP surgery may impact on patient outcomes. Some specific features which could affect care delivery include motivation of surgery staff, or behaviour include

presence of a specialist diabetes nurse in the practice, deprivation levels in the neighbourhood of the surgery, staff to patient ratio and total numbers of consultations.

6.9.2 Future studies

According to the MRC framework for complex interventions (1, 32, 33), evaluating an intervention to reveal all the processes and mechanisms involved is an iterative process, which may involve several feasibility and pilot studies. Before a large-scale definitive study of POC HbA_{1c} testing is undertaken, further preparatory work is needed to better understand how POC testing could fit into different care pathways and identify how recruitment, follow-up and implementation may differ when used across a wider range of settings. Additionally, aspects of trial design which have not yet been tested, including randomisation and frequency of testing could be tested, and preliminary data on costs collected. Once these are better understood, a tailored approach to how the intervention could be delivered could be used. It is proposed to develop a training intervention, which could help clinicians organise their clinics most effectively, optimise patient care and provide an education package to patients. Here a plan for future work is suggested, which includes POC HbA_{1c} testing studies and intervention development. It is proposed that these would take place in three phases which would consist of a pilot study, development of a training intervention and a definitive trial (Figure 6.1). These are detailed below.

Figure 6.1 – Proposed future study plan.



Pilot study

This would be a randomised design to test the feasibility of the study design and explore implementation issues that may arise when POC testing is implemented more widely. Randomisation at the patient level rather than the practice level would make it possible to explore some of different issues with implementation which may arise across practices. These include the feasibility of linking POC analysers with multiple laboratories and collating these results, comparison of different models of clinic organisation (healthcare assistant testing followed by GP consultation, nurse-based testing and consultation, or multiple users within a single GP practice) and context (for examples, levels of

deprivation or urban settings). Data collected could include patient recruitment, follow-up, cross-contamination between randomised groups, delivery of the intervention, medication changes, HbA_{1c}, care pathways, appointment duration, costs, acceptability, satisfaction and adherence using both quantitative and qualitative methods.

Design and piloting of training intervention

A training package for clinicians and a patient education intervention which could be offered along with the POC testing could be designed by working with stakeholder groups (patients, clinicians, laboratory professionals, diabetes educators and industry representatives). The development of the training intervention for clinicians could be informed by some of the different models of care used in GP practices which participated in the pilot study to offer training packages tailored to the clinicians involved and the care model used. It could include guidance to assist with organisation of clinics, provide working models of how to re-structure care which could be effective, suggestions on how to provide feedback and education to patients, guidance on adjustment of medications if necessary, and guidelines on scheduling appropriate time interval for the follow-on appointment. The patient education package could include elements of feedback of the result, discussion of options and implications, target-setting and provision of printed materials and leaflets. These could then be piloted in a very small number of GP practices prior to scale-up for a large trial.

Definitive RCT

The POC testing combined with education package will be tested in a randomised trial to measure the effect on HbA_{1c}, hospitalisations, long-term outcomes (mortality and morbidity) and costs. The final design of the trial will be informed by data collected in the pilot study. A full health economic analysis will be conducted to compare POC testing

health resource use and its cost effectiveness with usual care. Longer-term follow-up of patients in the trial can continue by using linked data to collect morbidity and mortality outcomes after the trial has completed.

6.10 Summary

This research has found that HbA_{1c} testing varies across the year and is influenced by financial incentives to GPs. Regular monitoring of patients with less controlled diabetes may be easier if POC HbA_{1c} testing is used. It has been demonstrated that POC devices can be confidently used by nurses to manage less well-controlled diabetes patients. Although POC devices show large amounts of variability in performance compared with laboratory methods, the device used in the study received very positive feedback from both patients and clinicians. The main barrier to adopting these technologies is a perception of higher cost, but whether actual costs for delivering these tests are higher, is not clear. Nevertheless, changes in the funding or reimbursement mechanisms for POC testing would be necessary to encourage GP practices to use this type of testing. The main advantage of POC testing is the rapid availability of the test result; how this then changes clinical decisions, clinical pathways and behaviour will determine how it impacts on overall patient care. It remains to be seen whether POC HbA_{1c} testing will actually improve HbA_{1c} or patient outcomes; these would need to be evaluated in a longer-term randomised trial. However, before the definitive trial takes place, further preparatory work is needed.

6.11 Concluding remarks

One of the most important things I have learnt by carrying out this research is the value of combining different methodologies. In this study, the qualitative findings have been as informative as the quantitative findings. If I had chosen only to use quantitative methods I

would have needed to identify in advance, outcomes which I deemed to be important to measure. This work has made it clear to me that aspects of behaviour which contribute to the success of the intervention, or affect the way the intervention has been delivered, cannot easily be identified or measured without speaking to the people involved. The findings from this thesis go some way towards understanding the mechanisms and barriers to POC HbA_{1c} testing. This work will form a pivotal part in basing funding applications for a future clinical study on POC HbA_{1c} testing.

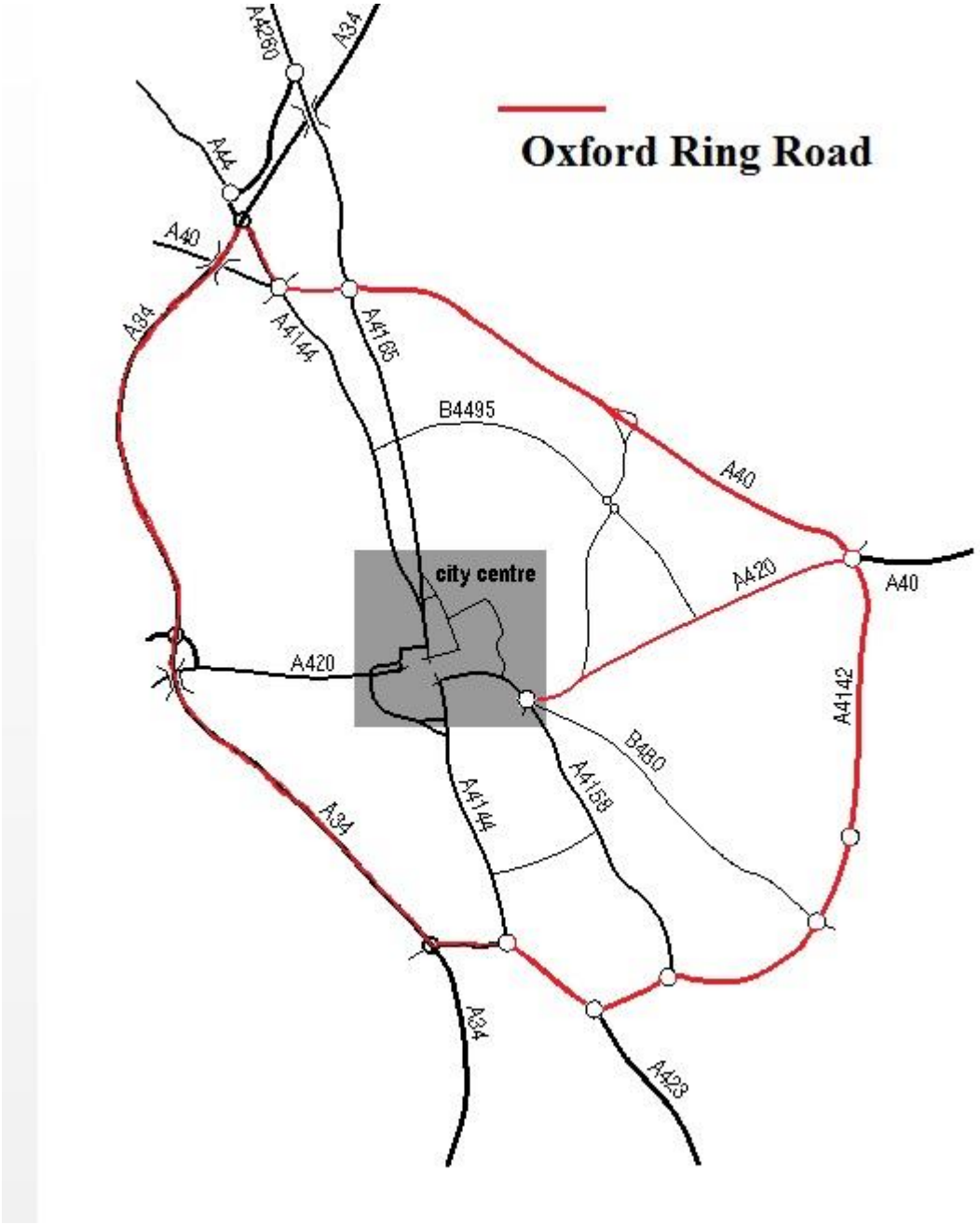
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Appendix 1 – Map and CPRD

Map showing Oxford ring road



Independent Scientific Advisory Committee CPRD protocol

Variation of HbA1c testing frequency with patient and GP factors – protocol for an analysis of the Clinical Practice Research Datalink

Jennifer Hirst, Richard Stevens, Andrew Farmer

Lay summary (200 words)

People with diabetes have regular testing of glycated haemoglobin (HbA1c) levels to monitor long-term blood glucose control. Guidelines recommend that HbA1c is re-tested every 2-6 months, but sometimes people have their HbA1c tested more frequently than every 2 months. GP practices receive money for testing HbA1c in their patients at least every 12 months, but some people have longer between their HbA1c tests. In this study we will look at how often people with diabetes have their HbA1c tested by their doctor and whether HbA1c is tested less than 60 days or more than a year from the previous test. We will use tables and graphs and statistical models to see how testing HbA1c too frequently (or not frequently enough) differs with the time of year the test was done and look at whether people's sex, age or the medicines they are taking affect how often they are tested. We will also look at whether people admitted to hospital or who died were more likely to have their HbA1c tested recently or whether it was a long time since their previous HbA1c test. This work will help us understand what affects HbA1c testing frequency and how these affect patient outcomes.

Scientific summary

Glycated haemoglobin (HbA1c) is used to monitor glycaemic control in diabetes. NICE guidelines recommend re-testing HbA1c every 2-6 months but these are not always followed. The quality and outcomes framework (QOF) reimburses General Practices (GP) to measure indicators including HbA1c and blood pressure in people with diabetes annually. A recent analysis of hospital data by our team found that significantly more repeat HbA1c tests are taking place within 60 days of the previous test in the 4 months immediately prior to the QOF deadline on 31st March than over the rest of the year. This may be because patients who have HbA1c over QOF thresholds and are thus not meeting targets are more likely to be recalled for tests earlier in the months leading up to the QOF assessment dates than over the rest of the year. In our proposed analysis we will describe how many HbA1c tests take place outside of guidelines (defined as <60 days or >366 days from the previous test). We will use multilevel logistic regression to examine whether re-testing HbA1c within 60 days is associated with the time of year relative to assessment dates for GP reimbursement as well as other patient and GP-level factors. We will also examine whether there is an association between patient hospitalisation or mortality and the time since the previous HbA1c test. We will categorise GP practices into those that test HbA1c more frequently and those that test less frequently and compare hospitalisation and mortality rates between GP practices using a Poisson regression model.

Background

Diabetes is a growing problem with a prevalence of 6.1% in the UK, costing the NHS £13.8 billion each year (1, 2). Poor glycaemic control is linked to the development of health complications which account for around 80% of total diabetes-related costs through treatments and hospitalisations. In comparison diabetes care through monitoring and appropriate use of medications is cheap (1) and reduces the incidence of complications (2-5). Maintaining good glycaemic control is an essential part of diabetes care and is achieved through regular monitoring of glycated haemoglobin (HbA1c), a measure of the average blood glucose over the preceding 3 months (6), and management with glucose-lowering medications. The National Institute for Health and Care Excellence (NICE) guidelines recommend testing HbA1c at 2 to 6 monthly intervals in people with type 2 diabetes (7) which are similar to guidelines in other countries (8, 9). The evidence cited to support this testing interval is a combination of the assumed 120-day life-span of a red blood cell (10), which can vary considerably between patients (11), and expert opinion. Although there is no consensus on what the optimal frequency for HbA1c testing is (12) it generally thought that there is no value in repeating an HbA1c test within 3 months. The Quality and Outcomes Framework (QOF) is an incentive scheme which has been running since 2004 in the UK and reimburses General Practitioners (GPs) based on patient health indicators; evaluation of the criteria takes place on 31st March. For diabetes these include monitoring patients' blood pressure and HbA1c every 12 months (13) and achieving target levels. This should encourage practices to monitor their patients' HbA1c at least annually and may have an impact on testing intervals.

Several recent reports suggest that guidelines for HbA1c testing are not always adhered to (14-16). An analysis of HbA1c requests carried out using laboratory data from a hospital in Singapore (16) reported that 42% of HbA1c test requests made to the hospital lab in 2006 and 2007 took place less than 90 days from the previous request. In the UK an analysis of HbA1c test requests over a 10-year period from 2001 to 2011 in a North Staffordshire hospital in the UK (15) found that over 50% of all test requests were made either sooner or later than recommended by guidelines, the majority of which came from primary care. Similar results had been observed in an earlier analysis of diabetes out-patient clinic data in Turkey conducted in 2002 to 2004 (14). An analysis of newly diagnosed patients with type 2 diabetes followed up for 10 years from a British Primary Care database (17) suggests that around 23% of people with HbA1c above 7% did not have their HbA1c re-tested within 7 months. A recent Diabetes UK publication reports that although in 2012-2013 more than 90% of people with diabetes had an annual HbA1c check this figure was much lower in people with type 1 diabetes (80%) than for those with type 2 diabetes (94%) (18). In the United States a recent report of hospital data by the College of American Pathologists found that the majority of patients had fewer than 8 HbA1c tests in 24 months, suggesting that HbA1c is not tested more frequently than every 3 months (19). These reports suggest that guidelines do not always have an impact on patterns of HbA1c testing. In addition to this there is now evidence that testing HbA1c at

more frequent time intervals can detect clinically significant changes in HbA1c in people who have had a recent medication change (20). Having more frequent HbA1c tests may therefore be beneficial to some patients, particularly those who have had a recent medication change, to monitor response to medication and adherence.

Work recently carried out by our team in Oxford to analyse patterns in HbA1c tests performed in the John Radcliffe Hospital in Oxford over the past 10 years (unpublished) has shown that over 20% of all test requests are carried out outside recommended intervals. Testing outside recommended intervals was found to be significantly associated with a number of factors including test date and location of GP practice. Of particular interest was the finding that repeat testing within 60 days was more common in the 4 months prior to the QOF assessment date (December to March) compared with the other 8 months of the year. This may be because patients who have HbA1c over QOF thresholds and are thus not meeting targets are more likely to be recalled for tests sooner in the months just prior to the QOF assessment dates than over the rest of the year. This analysis was however limited because we did not have access to GP records and could not therefore ascertain whether patients had a diagnosis of diabetes or details of any medications taken. We would now like to extend the analysis further to establish whether more frequent HbA1c testing in the months prior to QOF is also seen in national data and compare testing frequency pre- and post- the introduction of QOF in 2004. Because there may be differences in HbA1c testing between England, Scotland and Wales, or differences between testing rates in London and the south of England compared with the north we would like to explore potential associations between testing frequency and geographic location, as well as medication use and differences between insulin and non-insulin users. Recent work carried out at the University Hospital of North Midlands found an association between hospital admissions and mortality with how recently patients had had their previous HbA1c measured (21). We would like to follow up this work to assess whether there are any associations with hospitalisations and mortality (diabetes-related and non-diabetes related) at a national level. In addition to this we would like to explore potential associations between hospitalisation and mortality rates in GP practices that test HbA1c more frequently and those that test less frequently.

Aims, objectives and rationale

Aim: To establish which factors are associated with the frequency and timing of HbA1c test requests from General Practice (GP) in the UK.

Objectives:

1. To describe the frequency and timing of HbA1c testing in GP practices.
2. To explain how HbA1c testing frequency varies with time of year in relation to QOF assessment dates and patient and GP-level factors.
3. Establish whether mortality and hospitalisations are associated with the timing of the previous HbA1c test and testing behaviour of GP practices.

Rationale

Regular HbA1c testing is crucial to good diabetes care. There is evidence from previous reports that test utilisation is not always taking place at intervals recommended by guidelines (15, 22, 23), however these studies have been carried out using hospital laboratory data where it is neither possible to confirm whether patients had a diagnosis of diabetes nor to explore potential associations between medication use and HbA1c testing. We would now like to extend these analyses to examine patterns in HbA1c testing nationally and explore whether QOF assessment influences the frequency and timing of HbA1c testing in primary care and other factors which may influence testing frequency including geographic variations in HbA1c monitoring. Moreover we would be able to examine whether diabetes-related hospitalisations and mortality are associated with the timing of the previous HbA1c test or the rate of testing in the GP practice. An analysis of CPRD data would provide a comprehensive overview of patient and GP-level factors which may be associated with HbA1c testing frequency to guide policy makers.

Study type

Descriptive, hypothesis testing and hypothesis generating

Study design

Retrospective cohort study of 100,000 patients with diabetes.

Sample size

In a cohort of 100,000 diabetes patients with multiple HbA1c measures it is estimated that 10% will have type 1 diabetes (24). Of the remaining 90,000 with type 2 diabetes around 43% will be insulin users (24). This will leave over 50,000 patients with type 2 diabetes who are non-insulin users. Our main analysis is testing whether re-testing HbA1c within 60 days is more frequent between the months of December and March compared with April to November: assuming there is a mean of 8 tests per patient over the 10 years (based on our previous work with hospital laboratory data) this will give a total of 400,000 HbA1c tests in non-insulin users, 350,000 of which are repeat tests. If only 2% of tests were repeated within 60 days (a conservative estimate) this would equate to 7000. From previous work on hospital data the odds ratio for testing Dec-Mar was 1.12, which would give a 95% confidence interval of 1.07 to 1.18 in our new dataset; sufficient to detect a significant result.

The analysis of hospitalisations and mortality will use similar methods to a previously reported analysis (21) of hospitalisations and time since previous HbA1c test which found significant association for a total of 3161 hospital admissions. In our proposed cohort of 100,000 diabetes patients, around 50,000 will be non-insulin users and if we have similar levels to other studies we may expect around 11,000 diabetes-related deaths over the 10-

year follow-up (25, 26) and a larger number of hospital admissions. There would therefore be sufficient events to detect differences between groups.

Study population

Inclusion criteria:

Adults (>18 years) with a diagnosis of diabetes (defined as one or more of the medcodes listed in Appendix 1, or those using product codes listed in Appendix A2). Diabetes diagnosis can be pre-existing or take place at any point between 1st January 2005 and 31st December 2014.

In patients with existing diabetes the index HbA1c test is defined as the first HbA1c test after 1st January 2005; included patients must have had a minimum of 2 HbA1c tests prior to the index test date and post diagnosis.

Patients with incident diabetes over the 10 years follow up from Jan 2005 to Dec 2014 will also be included; these patients must have a minimum of 3 HbA1c test results post diagnosis, the second HbA1c test is defined as the index test date in these patients.

Exclusion criteria:

Ambiguously recorded gender

Patients with gestational diabetes, malnutrition-related diabetes, MODY, Bronzed diabetes or steroid-induced diabetes (see Appendix A3)

Patients with fewer than 3 HbA1c measures in total.

Patients with cancer and end-stage renal disease (Appendix A4 and A5)

Exposures

The exposure is HbA1c testing post diagnosis of diabetes.

Outcomes

Primary outcome is HbA1c testing interval. For the main, hypothesis testing analyses, this will be coded as short interval (<60 days) or longer interval. Secondary outcomes include HbA1c values, identified using entity code 275 [HbA1c – Diabetic control].

Covariates

Covariates to be examined will be age, sex, previous HbA1c, absolute change in HbA1c between the two previous measures, year, baseline body mass index (BMI), blood pressure and total cholesterol measures, smoking status, diagnosis of microalbuminuria or nephropathy, type of diabetes, medication status (diet alone, single oral, multiple oral medications-including exenatide or insulin), medication change at previous visit, prescription for lipid-lowering or antihypertensive medication , GP practice, geographic

regions (Scotland, Wales, England, and regionally within England), deprivation score of GP practice (linked to ONS data) and recent medication change.

For covariates which can change over time such as BMI or blood pressure, the closest value from up to two years prior to the index test date will be used, cases in which no values are available within this time frame will be treated as missing data.

Linked data

Data on hospitalisations, death and deprivation score will be requested. Office for National Statistics (ONS) data linkage will be required to ascertain whether the cause of death or hospitalisations may be diabetes-related. The deprivation score will be used as a covariate in the logistic regression to explain HbA1c testing frequency.

Statistical analysis plan

Stata 12.1 SE will be used to carry out all statistical analyses. Results will be reported as mean and standard deviation. Levels of significance between groups were tested using two-sample t-test and tests of proportions.

3. Descriptive analysis

Descriptive data on patient age, sex, types of diabetes medication, body mass index (BMI), blood pressure (BP), mean HbA1c, mean testing intervals and numbers of tests less than 60 days or more than 366 days from the previous test will be presented in tables for all patients and for subgroups stratified by age, sex, previous HbA1c, type of diabetes and insulin use. The number of tests performed each year and the mean numbers of test requests for each month of the 10-year follow-up will be represented graphically in bar charts. Numbers of HbA1c tests taking place at different time intervals from the previous test will be tabulated within subgroups of patients categorised by previous HbA1c: patients with HbA1c<6.5% will be defined as tightly controlled diabetes, patients with HbA1c≥6.5% and <7.5% will be classed as having well controlled diabetes, and patients with HbA1c≥7.5% as uncontrolled diabetes. The numbers of test requests taking place within time intervals recommended by guidelines and those taking place <60 days or >366 days from the previous test in 2-year periods throughout the 10 years from 1st January 2005 to 31st December 2014 will be reported so trends over time can be explored. In each of these 2-year periods the total number of patients with fewer than 3 tests, fewer than 4 tests and more than 8 tests will be reported.

Comparison of rates of HbA1c testing between those with type 1 and type 2 diabetes will be tabulated, as well as comparison in testing between different geographic location (England, Scotland, Wales and different regions of the England).

Change in HbA1c will be plotted against HbA1c testing interval stratified by previous HbA1c (categorised into <6.5%, 6.5-7.5% and >7.5%) using methods described by Driskell and colleagues (22).

4. Multi-level logistic regression models

We will carry out all analyses on the whole cohort of included patients, but also separately for type 1 and type 2 diabetes and for those with type 2 diabetes who are insulin users and non-insulin users. Univariate and mulitvariate analyses will be conducted in the 10 years of patient data from 1st January 2005 to 31st December 2014: a 3-level mixed effects model will be used to account for multiple measures in each patient nested within each GP practice.

(iii) In a hypothesis-testing analysis stepwise univariate and multivariate logistic regression will be used to examine (a) whether patient-level and (b) GP practice level factors are associated with HbA1c testing intervals <60 day (or >366 days) from the previous test. The relationship between time of year (Dec-Mar vs Apr-Nov) and time of year in combination with previous HbA1c>7.5% (or 58 mmol/mol) will be reported as odds ratios and 95% confidence intervals. To examine whether HbA1c testing intervals differ before and after the introduction of QOF in 2004 the logistic regression will also be conducted in a separate comparator group of patients selected using the same criteria from 1999 to 2004.

(iv) In a hypothesis-generating analysis patient and GP practice level factors will be examined and the odds ratios and 95% confidence intervals will be reported as hypothesis-generating analyses with re-testing HbA1c at <60 day (or >366 day) test intervals. Covariates to be examined will be:

- Age
- Sex
- previous HbA1c
- absolute change in HbA1c between the two previous measures
- year
- baseline BMI
- blood pressure and total cholesterol measures
- smoking status
- diagnosis of microalbuminuria or nephropathy
- type of diabetes
- medication change at previous visit
- prescription for lipid-lowering or antihypertensive medication
- GP practice, geographic regions (Scotland, Wales, England, and regionally within England)
- deprivation score of GP practice (linked to ONS data)
- medications taken (where appropriate - diet, insulin, single oral and multiple oral medications) and
- recent medication change

The fit of each covariate into the model will be tested based on a p value of <0.05. A sensitivity analysis will be carried out using a simple logistic regression model based on the time interval between two randomly selected sequential HbA1c measurements for each patient, to ensure that results are robust. A separate 1-level logistic regression model will be used to evaluate whether numbers of tests per person year are associated with GP-level factors: deprivation score and the location of GP practice.

5. Hospitalisation and mortality

(i) The mean HbA1c testing interval for each GP practice will be calculated, GP practices will then be categorised as "frequent testers" who re-test every 3-5 months, "moderate testers" who re-test every 5-8 months, and "infrequent testers" who re-test every 8-12 months. Mortality rates and numbers of hospitalisations within each of these 3 groups will be tabulated and differences will be tested for significance using logistic regression for mortality data and Poisson regression for count data (hospitalisations). Negative binomial regression may be used in place of Poisson regression depending on data dispersion.

(ii) A matched case-control design will be used to explore whether the length of time since the previous HbA1c test is associated with diabetes-related and all-cause hospitalisations and mortality. For each outcome (hospitalisation or mortality) a matched control within the same GP practice will be identified, matched on age, sex and diabetes medication type who was not hospitalized (or did not die) on the same day. The timing of the previous HbA1c test will be stratified into groups of < 3 months, 3-6 months, 6-12 months and > 12 months prior to the event. The time from the previous test will then be used in conditional logistic regression models to explain all-cause and diabetes-related hospitalisations and mortality.

Patients will remain in the analysis until the end of follow-up on 31st December 2014 or when they leave the surgery or die.

Missing data

By definition each patient included in the cohort will have a minimum of 3 HbA1c measurements. We expect age, sex, type of diabetes and medication status to be well recorded in the cohort. We will assume that anybody without a recorded smoking status is a non-smoker and those without (micro-) albuminuria or proteinuria measures to be disease-free. BMI, blood pressure and cholesterol are non-crucial to this analysis and will only be analysed in complete cases.

Patient/user group involvement

This protocol has been discussed with and reviewed by members of a diabetes Patient and Public Involvement group (PPI).

Limitations of study design

There are limitations which are inherent to using CPRD data which include misclassification and loss to follow-up. Covariates used in the analysis including BMI, blood pressure and smoking status will be based on baseline levels, and may change during the follow-up time.

This analysis will predominately categorise people as having received HbA1c tests outside recommended intervals, though it is likely that we will include people in the analysis who

have legitimate reasons for more or less frequent testing. We will attempt to minimise this by excluding people with life-threatening illnesses and pregnancy where reported.

Dissemination plan

The results from this work will be presented at scientific conferences or meeting and will be published in a high quality peer-reviewed medical journal.

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Medical and product codes for CPRD analysis

Diabetes medical codes

medcode	readcode	readterm
9897	9OL..00	Diabetes monitoring admin
3550	66A..00	Diabetic monitoring
6125	66AS.00	Diabetic annual review
2379	9N1Q.00	Seen in diabetic clinic
711	C10..00	Diabetes mellitus
13194	9OL4.00	Diabetes monitoring 1st letter
26666	2G5E.00	O/E - Right diabetic foot at low risk
26667	2G5I.00	O/E - Left diabetic foot at low risk
608	66A2.00	Follow-up diabetic assessment
11094	9NND.00	Under care of diabetic foot screener
12506	66AP.00	Diabetes: practice programme
18311	68A7.00	Diabetic retinopathy screening
13197	9OL1.00	Attends diabetes monitoring
101177	66At.00	Diabetic dietary review
13195	9OL5.00	Diabetes monitoring 2nd letter
95994	66Aq.00	Diabetic foot screen
11471	8B3l.00	Diabetes medication review
13067	66AZ.00	Diabetic monitoring NOS
13104	2BBK.00	O/E - no left diabetic retinopathy
13100	2BBJ.00	O/E - no right diabetic retinopathy
31157	2G5F.00	O/E - Right diabetic foot at moderate risk
10977	66Ac.00	Diabetic peripheral neuropathy screening
31156	2G5J.00	O/E - Left diabetic foot at moderate risk
2378	66AJ.00	Diabetic - poor control
8836	66AR.00	Diabetes management plan given
11348	9h42.00	Excepted from diabetes quality indicators: Informed dissent
1323	F420.00	Diabetic retinopathy
28873	66Ai.00	Diabetic 6 month review
13192	9OLA.00	Diabetes monitor. check done
7069	F420000	Background diabetic retinopathy
12030	9OL6.00	Diabetes monitoring 3rd letter
13074	13B1.00	Diabetic diet
12213	8BL2.00	Patient on maximal tolerated therapy for diabetes
9145	9N4I.00	DNA - Did not attend diabetic clinic
11041	9h41.00	Excepted from diabetes qual indicators: Patient unsuitable
8842	66A5.00	Diabetic on insulin
9974	9N1v.00	Seen in diabetic eye clinic
11433	2BBP.00	O/E - right eye background diabetic retinopathy
11129	2BBQ.00	O/E - left eye background diabetic retinopathy
17817	7L19800	Subcutaneous injection of insulin

13057	679L.00	Health education - diabetes
13071	66AI.00	Diabetic - good control
12675	66AQ.00	Diabetes: shared care programme
13196	66AD.00	Fundoscopy - diabetic check
47032	8CS0.00	Diabetes care plan agreed
8414	8CA4100	Pt advised re diabetic diet
6813	1434	H/O: diabetes mellitus
31171	2G5G.00	O/E - Right diabetic foot at high risk
31172	2G5K.00	O/E - Left diabetic foot at high risk
102490	66Av.00	Diabetic assessment of erectile dysfunction
1038	C100011	Insulin dependent diabetes mellitus
22823	66Ab.00	Diabetic foot examination
47144	2BBM.00	O/E - diabetic maculopathy absent both eyes
11677	8H7r.00	Refer to diabetic foot screener
106218	9m0A.00	Declined diabetic retinopathy screening
12307	66AU.00	Diabetes care by hospital only
31141	9OL8.00	Diabetes monitor.phone invite
50175	66AW.00	Diabetic foot risk assessment
38078	66A9.00	Understands diet - diabetes
6430	9NM0.00	Attending diabetes clinic
9958	42W..00	Hb. A1C - diabetic control
30648	9N4p.00	Did not attend diabetic retinopathy clinic
1647	C108.00	Insulin dependent diabetes mellitus
12262	8I3X.00	Diabetic retinopathy screening refused
3837	F420400	Diabetic maculopathy
31240	9OL7.00	Diabetes monitor.verbal invite
14889	C100111	Maturity onset diabetes
13070	66A1.00	Initial diabetic assessment
10642	ZC2C800	Dietary advice for diabetes mellitus
21689	13AB.00	Diabetic lipid lowering diet
47011	8Hj0.00	Referral to diabetes structured education programme
20900	9OLA.11	Diabetes monitored
10824	9N1i.00	Seen in diabetic foot clinic
31241	9OLZ.00	Diabetes monitoring admin NOS
18824	8I3W.00	Diabetic foot examination declined
35383	9OLD.00	Diabetic patient unsuitable for digital retinal photography
95124	9Oy0.00	Diabetes screening invitation
12247	8I6G.00	Diabetic foot examination not indicated
14803	C100100	Diabetes mellitus, adult onset, no mention of complication
17236	14P3.00	H/O: insulin therapy
93854	9OLM.00	Diabetes structured education programme declined
13069	66A8.00	Has seen dietician - diabetes
102434	66Au.00	Diabetic erectile dysfunction review
1682	C101.00	Diabetes mellitus with ketoacidosis
10755	F420600	Non proliferative diabetic retinopathy
22130	9OL3.00	Diabetes monitoring default
18167	66AT.00	Annual diabetic blood test

52237	9360	Patient held diabetic record issued
16230	C106.00	Diabetes mellitus with neurological manifestation
20696	66AA.11	Injection sites - diabetic
19739	68A9.00	Diabetic retinopathy screening offered
16490	66AH.00	Diabetic treatment changed
18747	8I6F.00	Diabetic retinopathy screening not indicated
13191	9OL..11	Diabetes clinic administration
13108	2BBX.00	O/E - left eye diabetic maculopathy
13102	2BBW.00	O/E - right eye diabetic maculopathy
93870	8Hj5.00	Referral to XPERT diabetes structured education programme
32619	66Af.00	Patient diabetes education review
7795	C106.12	Diabetes mellitus with neuropathy
7777	8H4F.00	Referral to diabetologist
2342	F372.12	Diabetic neuropathy
3286	F420100	Proliferative diabetic retinopathy
18505	C108.11	IDDM-Insulin dependent diabetes mellitus
103772	8CE0200	Insulin passport given
12682	679R.00	Patient offered diabetes structured education programme
94647	9Oy..00	Diabetes screening administration
13078	13AC.00	Diabetic weight reducing diet
26604	66AY.00	Diabetic diet - good compliance
61021	68AB.00	Diabetic digital retinopathy screening offered
64142	8Hl1.00	Referral for diabetic retinopathy screening
103762	8BAi.00	Insulin passport completed
17095	2G5A.00	O/E - Right diabetic foot at risk
12225	8H7C.00	Refer, diabetic liaison nurse
8618	ZLA2500	Seen by diabetic liaison nurse
63412	8CR2.00	Diabetes clinical management plan
18066	8CE0.00	Diabetic leaflet given
101456	8IAs.00	Diabetic dietary review declined
26664	2G5B.00	O/E - Left diabetic foot at risk
11599	7276	Pan retinal photocoagulation for diabetes
17886	66AM.00	Diabetic - follow-up default
8306	8H7f.00	Referral to diabetes nurse
11018	8HBG.00	Diabetic retinopathy 12 month review
2986	F420200	Preproliferative diabetic retinopathy
19381	8HTk.00	Referral to diabetic eye clinic
13099	2BBR.00	O/E - right eye preproliferative diabetic retinopathy
13103	2BBS.00	O/E - left eye preproliferative diabetic retinopathy
105740	2G5d.00	O/E - Left diabetic foot at increased risk
35316	2G5H.00	O/E - Right diabetic foot - ulcerated
105741	2G5e.00	O/E - Right diabetic foot at increased risk
28574	9h4..00	Exception reporting: diabetes quality indicators
35116	2G5L.00	O/E - Left diabetic foot - ulcerated
9835	2BBL.00	O/E - diabetic maculopathy present both eyes
83485	66Am.00	Insulin dose changed
2475	C104.11	Diabetic nephropathy

12507	9N2i.00	Seen by diabetic liaison nurse
103816	8CE0100	Insulin alert patient information booklet given
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder
68546	ZRB4.00	Diabetes clinic satisfaction questionnaire
54601	9NN8.00	Under care of diabetologist
82474	8Hl4.00	Referral to community diabetes specialist nurse
13097	2BBT.00	O/E - right eye proliferative diabetic retinopathy
9881	M271200	Mixed diabetic ulcer - foot
11930	9NN9.00	Under care of diabetes specialist nurse
38986	C100.00	Diabetes mellitus with no mention of complication
13101	2BBV.00	O/E - left eye proliferative diabetic retinopathy
17067	F171100	Autonomic neuropathy due to diabetes
106679	8OA3.00	Provision of written information about diabetes and driving
38103	9N0m.00	Seen in diabetic nurse consultant clinic
24327	M271000	Ischaemic ulcer diabetic foot
14050	42c..00	HbA1 - diabetic control
32739	9N0n.00	Seen in community diabetes specialist clinic
106332	9m00.00	Eligible for diabetic retinopathy screening
11977	ZL62500	Referral to diabetes nurse
105585	8CMW700	Diabetes clinical pathway
11626	F420z00	Diabetic retinopathy NOS
96010	66Ap.00	Insulin treatment initiated
26605	9OLB.00	Attended diabetes structured education programme
46521	9N2d.00	Seen by diabetologist
11663	M271100	Neuropathic diabetic ulcer - foot
98954	3883	Diabetes treatment satisfaction questionnaire
22967	2BBF.00	Retinal abnormality - diabetes related
33254	C105.00	Diabetes mellitus with ophthalmic manifestation
10659	F464000	Diabetic cataract
25636	66Aa.00	Diabetic diet - poor compliance
54419	918T.00	Diabetes key contact
38129	9N0o.00	Seen in community diabetic specialist nurse clinic
16502	C104.00	Diabetes mellitus with renal manifestation
57389	93C4.00	Patient consent given for addition to diabetic register
31790	F372.00	Polyneuropathy in diabetes
24490	C100000	Diabetes mellitus, juvenile type, no mention of complication
22023	66AJz00	Diabetic - poor control NOS
101455	9OLN.00	Diabetes monitor invitation by SMS (short message service)
26603	9OL2.00	Refuses diabetes monitoring
7059	8H2J.00	Admit diabetic emergency
106723	9Oy0200	Diabetic foot screening invitation first letter
93631	9OLL.00	XPERT diabetes structured education programme completed
2478	66AJ100	Brittle diabetes
94955	9NiE.00	Did not attend XPERT diabetes structured education programme
107423	661N400	Diabetes self-management plan review
24363	8A13.00	Diabetic stabilisation
96143	9kL..00	Insulin initiation - enhanced services administration

9013	66AJ.11	Unstable diabetes
57723	8HHy.00	Referral to diabetic register
51261	C10E.12	Insulin dependent diabetes mellitus
27891	N030100	Diabetic Charcot arthropathy
13678	ZL62600	Referral to diabetic liaison nurse
10099	F420300	Advanced diabetic maculopathy
12703	3881	Education score - diabetes
18056	2G5C.00	Foot abnormality - diabetes related
102768	9NiZ.00	Did not attend diabetes foot screening
103761	671F000	Insulin alert pat information booklet information discussed
100436	679L000	Education in self management of diabetes
94699	ZRB5.00	Diabetes treatment satisfaction questionnaire
43951	66AK.00	Diabetic - cooperative patient
36669	66b1.00	Diabetic monitoring not required
104858	8BAm.00	Insulin passport checked
7328	M037200	Cellulitis in diabetic foot
93704	8Hj3.00	Referral to DAFNE diabetes structured education programme
2340	F381311	Diabetic amyotrophy
50972	C100z00	Diabetes mellitus NOS with no mention of complication
68818	ZRB5.11	DTSQ - Diabetes treatment satisfaction questionnaire
31310	C108900	Insulin dependent diabetes maturity onset
29041	66AN.00	Date diabetic treatment start
107414	8I94.00	Diabetes structured education programme not available
94011	9OLG.00	Attended XPERT diabetes structured education programme
101728	66As.00	Diabetic on subcutaneous treatment
94186	9OLF.00	Diabetes structured education programme completed
102549	66Aw.00	Insulin dose
38076	M21yC00	Insulin lipohypertrophy
66475	66Ak.00	Diabetic monitoring - lower risk albumin excretion
27921	2G51000	Foot abnormality - diabetes related
6791	C108800	Insulin dependent diabetes mellitus - poor control
46533	13Y1.00	Diabetic association member
66274	66Ah.00	Insulin needles changed for each injection
16881	ZV65312	[V]Dietary counselling in diabetes mellitus
49884	6761	Diabetic pre-pregnancy counselling
35785	F372100	Chronic painful diabetic neuropathy
107464	66AS000	Diabetes Year of Care annual review
5002	F372.11	Diabetic polyneuropathy
15690	C103.00	Diabetes mellitus with ketoacidotic coma
42505	C101z00	Diabetes mellitus NOS with ketoacidosis
16946	13L4.11	Diabetic child
37315	F3y0.00	Diabetic mononeuropathy
38130	ZRB6.00	Diabetes wellbeing questionnaire
35107	C104z00	Diabetes mellitus with nephropathy NOS
17869	66AL.00	Diabetic-uncooperative patient
107361	679L200	Education about diabetes and driving
2471	K01x100	Nephrotic syndrome in diabetes mellitus

47341	8A12.00	Diabetic crisis monitoring
32403	C107.11	Diabetes mellitus with gangrene
18142	N030000	Diabetic cheiroarthropathy
104287	8Hlc.00	Referral to community diabetes service
22573	C106z00	Diabetes mellitus NOS with neurological manifestation
51697	C10G.00	Secondary pancreatic diabetes mellitus
6509	C108700	Insulin dependent diabetes mellitus with retinopathy
36798	7L10000	Continuous subcutaneous infusion of insulin
32359	ZRbH.00	Perceived control of insulin-dependent diabetes
94330	8H4e.00	Referral to diabetes special interest general practitioner
34152	G73y000	Diabetic peripheral angiopathy
50960	L180500	Pre-existing diabetes mellitus, insulin-dependent
45250	ZL22500	Under care of diabetic liaison nurse
44443	C108500	Insulin dependent diabetes mellitus with ulcer
18662	8HBH.00	Diabetic retinopathy 6 month review
61470	66Al.00	Diabetic monitoring - higher risk albumin excretion
17247	F35z000	Diabetic mononeuritis NOS
47370	8HLE.00	Diabetology D.V. done
106360	K27y700	Erectile dysfunction due to diabetes mellitus
24571	F372200	Asymptomatic diabetic neuropathy
39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation
43493	M21yC11	Insulin site lipohypertrophy
7045	14F4.00	H/O: Admission in last year for diabetes foot problem
47328	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
93491	9OLJ.00	DAFNE diabetes structured education programme completed
35321	8H3O.00	Non-urgent diabetic admission
93390	9OLH.00	Attended DAFNE diabetes structured education programme
47058	8Hg4.00	Discharged from care of diabetes specialist nurse
105302	K08yA00	Proteinuric diabetic nephropathy
34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
106269	9m0..00	Diabetic retinopathy screening administrative status
69163	8HTi.00	Referral to multidisciplinary diabetic clinic
102767	67IJ100	Pre-conception advice for diabetes mellitus
48078	F372000	Acute painful diabetic neuropathy
52041	2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
90301	66Ag.00	Insulin needles changed daily
58133	ZLD7500	Discharge by diabetic liaison nurse
105207	8HTE100	Referral to community diabetes clinic
105446	679c.00	Insulin administration education
106722	9Oy0300	Diabetic foot screening invitation second letter
47584	F420500	Advanced diabetic retinal disease
64357	C10zz00	Diabetes mellitus NOS with unspecified complication
32556	C107.12	Diabetes with gangrene
22487	C10N.00	Secondary diabetes mellitus
95636	C10ER00	Latent autoimmune diabetes mellitus in adult
94956	8I84.00	Did not complete XPERT diabetes structured education program
52212	Cyu2.00	[X]Diabetes mellitus

106953	8IEa.00	Referral to DAFNE diabetes structured educn prog declined
58639	8I57.00	Patient held diabetic record declined
28856	8CP2.00	Transition of diabetes care options discussed
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
95553	9NiA.00	Did not attend diabetes structured education programme
53634	R054200	[D]Gangrene of toe in diabetic
103798	9b92000	Diabetic medicine
53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
14049	42WZ.00	Hb. A1C - diabetic control NOS
48310	ZV6DA00	[V]Admitted for commencement of insulin
32770	44V3.00	Glucose tol. test diabetic
93380	C10N100	Cystic fibrosis related diabetes mellitus
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
67853	C106000	Diabetes mellitus, juvenile, + neurological manifestation
45491	C10z.00	Diabetes mellitus with unspecified complication
101834	9h43.00	Excepted from diabetes qual indicators: service unavailable
30477	F420700	High risk proliferative diabetic retinopathy
33343	C10y.00	Diabetes mellitus with other specified manifestation
16491	C106.13	Diabetes mellitus with polyneuropathy
26855	C108400	Unstable insulin dependent diabetes mellitus
49640	2G5W.00	O/E - left chronic diabetic foot ulcer
103817	8BAj.00	Informed dissent not to carry insulin passport
61523	C106y00	Other specified diabetes mellitus with neurological comps
17313	F440700	Diabetic iritis
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
99277	9NiC.00	Did not attend DAFNE diabetes structured education programme
44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
50937	8HTe.00	Referral to diabetes preconception counselling clinic
52630	2BBo.00	O/E - sight threatening diabetic retinopathy
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication
31053	R054300	[D]Widespread diabetic foot gangrene
35105	C104100	Diabetes mellitus, adult onset, with renal manifestation
44033	F345000	Diabetic mononeuritis multiplex
55431	L180X00	Pre-existing diabetes mellitus, unspecified
61210	TJ23z00	Adverse reaction to insulins and antidiabetic agents NOS
33807	C107200	Diabetes mellitus, adult with gangrene
69152	66Aj.00	Insulin needles changed less than once a day
62384	2G5V.00	O/E - right chronic diabetic foot ulcer
100422	8HgC.00	Discharged from diabetes shared care programme
95094	8I81.00	Did not complete diabetes structured education programme
34541	8HVU.00	Private referral to diabetologist
65463	F420800	High risk non proliferative diabetic retinopathy
54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis
39420	F381300	Myasthenic syndrome due to diabetic amyotrophy
106352	9m06.00	Excluded from diabetic retinopathy screening as deceased
106350	9m05.00	Excluded from diabetic retinopathy screening as moved away
46963	C108000	Insulin-dependent diabetes mellitus with renal complications

101190	66AQ100	Declined consent for diabetes year of care programme
43453	C10C.00	Diabetes mellitus autosomal dominant
104669	8IF..00	Prof judgemnt not to engage pt wt insulin alert requirements
30247	TJ23000	Adverse reaction to insulins
39809	C108J00	Insulin dependent diab mell with neuropathic arthropathy
43857	C10M.00	Lipoatrophic diabetes mellitus
57333	N030011	Diabetic cheiropathy
34528	3882	Diabetes well being questionnaire
106738	9Oy0000	Diabetic foot screening invitation
38617	C101y00	Other specified diabetes mellitus with ketoacidosis
100533	66AQ000	Unsuitable for diabetes year of care programme
59903	C106.11	Diabetic amyotrophy
103743	8IE2.00	Diabetes care plan declined
107452	66o..00	Further diabetic monitoring
68928	TJ23.00	Adverse reaction to insulins and antidiabetic agents
56448	C108A00	Insulin-dependent diabetes without complication
57621	C108D00	Insulin dependent diabetes mellitus with nephropathy
107793	9Oy0400	Diabetic foot screening invitation third letter
49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
67664	ZRBa.00	Education score - diabetes
70821	C10yz00	Diabetes mellitus NOS with other specified manifestation
13279	C104y00	Other specified diabetes mellitus with renal complications
45276	C10E312	Insulin dependent diabetes mellitus with multiple complicat
51066	9OLC.00	Family/carer attended diabetes structured education prog
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
52104	C108300	Insulin dependent diabetes mellitus with multiple complicatn
65684	U602311	[X] Adverse reaction to insulins and antidiabetic agents
69124	C107300	IDDM with peripheral circulatory disorder
95813	9N1o.00	Seen in multidisciplinary diabetic clinic
105937	8IEQ.00	Referral to community diabetes specialist nurse declined
106328	9m07.00	Excluded diabetc retinop screen as under care ophthalmolgist
106441	9m01.00	Ineligible for diabetic retinopathy screening
46290	C108y00	Other specified diabetes mellitus with multiple comps
60499	C108600	Insulin dependent diabetes mellitus with gangrene
61557	8HKE.00	Diabetology D.V. requested
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
64283	C10zy00	Other specified diabetes mellitus with unspecified comps
72702	C10E812	Insulin dependent diabetes mellitus - poor control
63364	U602312	[X] Adverse reaction to insulins
10098	C10yy00	Other specified diabetes mellitus with other spec comps
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation
94383	C10N000	Secondary diabetes mellitus without complication
106329	9m08.00	Excluded from diabetic retinopathy screening as blind
107739	679L211	Advice about diabetes and driving
65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma

68792	C10z000	Diabetes mellitus, juvenile type, + unspecified complication
47377	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
68714	SL23.00	Insulins and antidiabetic poisoning
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy
97849	C10E912	Insulin dependent diabetes maturity onset
106445	9m0E.00	Excluded from diabetic retinopathy screen physical disorder
42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
97809	8I82.00	Did not complete DAFNE diabetes structured education program
54600	C10E412	Unstable insulin dependent diabetes mellitus
91164	ZRB4.11	CSQ - Diabetes clinic satisfaction questionnaire
95539	C10FS00	Maternally inherited diabetes mellitus
101881	2BBr.00	Impaired vision due to diabetic retinopathy
41686	Cyu2000	[X]Other specified diabetes mellitus
65616	C108H00	Insulin dependent diabetes mellitus with arthropathy
100033	U60231E	[X] Adverse reaction to insulins and antidiabetic agents NOS
108655	8BAp.00	Insulin passport not checked
108993	661M400	Diabetes self-management plan agreed
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
59288	C103y00	Other specified diabetes mellitus with coma
64446	C108G00	Insulin dependent diab mell with peripheral angiopathy
64449	C108z00	Unspecified diabetes mellitus with multiple complications
102946	C10E012	Insulin-dependent diabetes mellitus with renal complications
43542	43Gk.00	Insulin antibody level
72333	8HME.00	Listed for Diabetology admissn
96506	C10G000	Secondary pancreatic diabetes mellitus without complication
98071	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
99628	Kyu0300	[X]Glomerular disorders in diabetes mellitus
99716	C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
99719	C10EA12	Insulin-dependent diabetes without complication
100292	Cyu2300	[X]Unspecified diabetes mellitus with renal complications
101311	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
106778	9m0C.00	Excluded frm diabetic retinopathy screen as terminal illness
108634	9NJy.00	In-house diabetic foot screening
106927	PKyP.00	Diab insipidus,diab mell,optic atrophy and deafness
70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
63337	43WQ.00	Insulin IgE antibody level
97824	ZRB6.11	DWBQ - Diabetes wellbeing questionnaire
98704	C10E512	Insulin dependent diabetes mellitus with ulcer
100770	C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
101735	C10E212	Insulin-dependent diabetes mellitus with neurological comps
102163	C10ED12	Insulin dependent diabetes mellitus with nephropathy
103935	1IA..00	No evidence of diabetic nephropathy
107597	9m0D.00	Excluded from diabetic retinopthy screen as learn disability
107881	K08yA11	Clinical diabetic nephropathy

109051	C10E612	Insulin dependent diabetes mellitus with gangrene
94098	43WR.00	Insulin IgG antibody level
758	C10F.00	Type 2 diabetes mellitus
1684	66A4.00	Diabetic on oral treatment
101801	66At100	Type II diabetic dietary review
506	C100112	Non-insulin dependent diabetes mellitus
7563	66A3.00	Diabetic on diet only
4513	C109.00	Non-insulin dependent diabetes mellitus
17859	C109.12	Type 2 diabetes mellitus
83532	66Ao.00	Diabetes type 2 review
28769	66AV.00	Diabetic on insulin and oral treatment
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus
93657	8Hj4.00	Referral to DESMOND diabetes structured education programme
11047	66AH000	Conversion to insulin
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
18219	C109.13	Type II diabetes mellitus
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
18278	C109J00	Insulin treated Type 2 diabetes mellitus
22884	C10F.11	Type II diabetes mellitus
12640	C10FC00	Type 2 diabetes mellitus with nephropathy
18496	C10F600	Type 2 diabetes mellitus with retinopathy
8403	C109700	Non-insulin dependent diabetes mellitus - poor control
95159	9NiD.00	Did not attend DESMOND diabetes structured education program
25627	C10F700	Type 2 diabetes mellitus - poor control
93529	9OLK.00	DESMOND diabetes structured education programme completed
47954	C10F900	Type 2 diabetes mellitus without complication
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis
25041	ZC2CA00	Dietary advice for type II diabetes
35397	C1A..00	Insulin resistance
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
36695	C10D.00	Diabetes mellitus autosomal dominant type 2
29979	C109900	Non-insulin-dependent diabetes mellitus without complication
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer
21482	C102.00	Diabetes mellitus with hyperosmolar coma
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy
58159	8I3k.00	Insulin therapy declined
18777	C10F000	Type 2 diabetes mellitus with renal complications
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
53392	C10F911	Type II diabetes mellitus without complication
102611	66At111	Type 2 diabetic dietary review
34268	C10F200	Type 2 diabetes mellitus with neurological complications
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis
53238	66AG.00	Diabetic drug side effects
44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract
95093	8I83.00	Did not complete DESMOND diabetes structured educat program

17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
49074	C10F400	Type 2 diabetes mellitus with ulcer
55123	66AO.00	Date diabetic treatment stopp.
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
64668	C10FJ11	Insulin treated Type II diabetes mellitus
37957	C10K.00	Type A insulin resistance
47315	C10F711	Type II diabetes mellitus - poor control
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
100791	66Ar.00	Insulin treatment stopped
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
108005	C109312	Type 2 diabetes mellitus with multiple complications
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
12736	C10F500	Type 2 diabetes mellitus with gangrene
59253	C10FG00	Type 2 diabetes mellitus with arthropathy
18264	C109J12	Insulin treated Type II diabetes mellitus
50609	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
24458	C109711	Type II diabetes mellitus - poor control
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications
45913	C109712	Type 2 diabetes mellitus - poor control
51939	ZV6DB00	[V]Admitted for conversion to insulin
43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
65267	C10F300	Type 2 diabetes mellitus with multiple complications
93727	C10FE11	Type II diabetes mellitus with diabetic cataract
49655	C10F611	Type II diabetes mellitus with retinopathy
56803	C107400	NIDDM with peripheral circulatory disorder
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus
58604	C109611	Type II diabetes mellitus with retinopathy
107331	66AH100	Conversion to insulin in secondary care
18209	C109012	Type 2 diabetes mellitus with renal complications
98723	C10FD11	Type II diabetes mellitus with hypoglycaemic coma
104639	C10FF11	Type II diabetes mellitus with peripheral angiopathy
55075	C109411	Type II diabetes mellitus with ulcer
102201	C10FC11	Type II diabetes mellitus with nephropathy
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps
42762	C109612	Type 2 diabetes mellitus with retinopathy
45919	C109212	Type 2 diabetes mellitus with neurological complications
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
65704	C109412	Type 2 diabetes mellitus with ulcer
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
103902	C10FG11	Type II diabetes mellitus with arthropathy
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene
24836	C109C12	Type 2 diabetes mellitus with nephropathy

43227	C10F311	Type II diabetes mellitus with multiple complications
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
48192	C109E11	Type II diabetes mellitus with diabetic cataract
95351	C10FA11	Type II diabetes mellitus with mononeuropathy
40962	C109H00	Non-insulin dependent d m with neuropathic arthropathy
43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
50225	C109011	Type II diabetes mellitus with renal complications
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
107508	66AH200	Conversion to insulin by diabetes specialist nurse
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
62107	C109511	Type II diabetes mellitus with gangrene
72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma
50527	C10FB11	Type II diabetes mellitus with polyneuropathy
54212	C109F00	Non-insulin-dependent d m with peripheral angiopath
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
46150	C109512	Type 2 diabetes mellitus with gangrene
64571	C109C11	Type II diabetes mellitus with nephropathy
91646	C10F411	Type II diabetes mellitus with ulcer
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy
57278	C10F011	Type II diabetes mellitus with renal complications
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
47409	C109B11	Type II diabetes mellitus with polyneuropathy
67905	C109211	Type II diabetes mellitus with neurological complications
100964	C10F111	Type II diabetes mellitus with ophthalmic complications
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma
59725	C109111	Type II diabetes mellitus with ophthalmic complications
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
98616	C10F211	Type II diabetes mellitus with neurological complications
109103	C109911	Type II diabetes mellitus without complication
18143	C109G11	Type II diabetes mellitus with arthropathy
49869	C109G12	Type 2 diabetes mellitus with arthropathy
50813	C109A11	Type II diabetes mellitus with mononeuropathy
104323	C10F511	Type II diabetes mellitus with gangrene
105784	C109912	Type 2 diabetes mellitus without complication
106061	C10FP11	Type II diabetes mellitus with ketoacidotic coma
106528	C10FN11	Type II diabetes mellitus with ketoacidosis
107701	C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
109197	C10FH11	Type II diabetes mellitus with neuropathic arthropathy
1549	C10E.00	Type 1 diabetes mellitus
17858	C108.12	Type 1 diabetes mellitus
102704	66At000	Type I diabetic dietary review
10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis

85660	66An.00	Diabetes type 1 review
24423	C108.13	Type I diabetes mellitus
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
18387	C10E700	Type 1 diabetes mellitus with retinopathy
10418	C10ED00	Type 1 diabetes mellitus with nephropathy
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
12455	C10E.11	Type I diabetes mellitus
35288	C10E800	Type 1 diabetes mellitus - poor control
55239	C10EQ00	Type 1 diabetes mellitus with gastroparesis
40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
104254	7L10011	Subcutaneous infusion with insulin pump
39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
104453	66At011	Type 1 diabetic dietary review
40682	C10E900	Type 1 diabetes mellitus maturity onset
22871	C10EP00	Type 1 diabetes mellitus with exudative maculopathy
69043	ZC2C900	Dietary advice for type I diabetes
54008	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
69676	C10EA00	Type 1 diabetes mellitus without complication
18683	C10E500	Type 1 diabetes mellitus with ulcer
43921	C10E400	Unstable type 1 diabetes mellitus
47582	C10E000	Type 1 diabetes mellitus with renal complications
62209	C10EM11	Type I diabetes mellitus with ketoacidosis
47650	C10E300	Type 1 diabetes mellitus with multiple complications
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy
42831	C10E200	Type 1 diabetes mellitus with neurological complications
49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract
46850	C108811	Type I diabetes mellitus - poor control
47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications
68390	C108512	Type 1 diabetes mellitus with ulcer
38161	C108711	Type I diabetes mellitus with retinopathy
42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma
96235	C10E911	Type I diabetes mellitus maturity onset
69993	C10E600	Type 1 diabetes mellitus with gangrene
95343	C10E711	Type I diabetes mellitus with retinopathy
18642	C10EH00	Type 1 diabetes mellitus with arthropathy
51957	C108511	Type I diabetes mellitus with ulcer
41049	C108712	Type 1 diabetes mellitus with retinopathy
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy
66872	C108D11	Type I diabetes mellitus with nephropathy
61829	C108212	Type 1 diabetes mellitus with neurological complications
93878	C10E511	Type I diabetes mellitus with ulcer
102112	C10E611	Type I diabetes mellitus with gangrene
21983	C108012	Type 1 diabetes mellitus with renal complications
49949	C10E411	Unstable type I diabetes mellitus
61344	C108011	Type I diabetes mellitus with renal complications
105337	C10E811	Type I diabetes mellitus - poor control
17545	C108F11	Type I diabetes mellitus with diabetic cataract

91942	C10E311	Type I diabetes mellitus with multiple complications
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
60107	C108411	Unstable type I diabetes mellitus
60208	C108J11	Type I diabetes mellitus with neuropathic arthropathy
68517	C10J.00	Insulin autoimmune syndrome
93468	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
45914	C108812	Type 1 diabetes mellitus - poor control
62613	C10EA11	Type I diabetes mellitus without complication
70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
97446	C108912	Type 1 diabetes mellitus maturity onset
97474	C108412	Unstable type 1 diabetes mellitus
49146	C108211	Type I diabetes mellitus with neurological complications
62352	C108H11	Type I diabetes mellitus with arthropathy
63017	C108911	Type I diabetes mellitus maturity onset
66145	C10EN11	Type I diabetes mellitus with ketoacidotic coma
91943	C10EC11	Type I diabetes mellitus with polyneuropathy
95992	C108A11	Type I diabetes mellitus without complication
97894	C10EP11	Type I diabetes mellitus with exudative maculopathy
99231	C108B11	Type I diabetes mellitus with mononeuropathy
99311	C10E111	Type I diabetes mellitus with ophthalmic complications
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria
102740	C108112	Type 1 diabetes mellitus with ophthalmic complications
108007	C108311	Type I diabetes mellitus with multiple complications
108724	C10EQ11	Type I diabetes mellitus with gastroparesis

Diabetes Product codes

5021	NovoRapid Penfill 100units/ml solution for injection 3ml cartridges (Novo Nordisk Ltd)
5015	NovoFine hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/30gauge (Novo Nordisk Ltd)
5142	BD Micro-Fine + hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (Becton, Dickinson UK Ltd)
5892	NovoRapid FlexPen 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
7228	NovoMix 30 FlexPen 100units/ml suspension for injection 3ml pre-filled pen (Novo Nordisk Ltd)
1589	U100 Insulin syringe 0.5ml
2454	Mixtard 30 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
5421	NovoFine hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge (Novo Nordisk Ltd)
5873	BD Micro-Fine + hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge (Becton, Dickinson UK Ltd)
36853	Lantus 100units/ml solution for injection 3ml pre-filled SoloStar pen (Sanofi)
1592	Actrapid penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
6958	Levemir FlexPen 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
1593	Insulatard penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
7266	Lantus 100units/ml solution for injection 3ml cartridges (Sanofi)
7267	NovoMix 30 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
6061	Novomix 30 30/70 100units/ml Injection (Novo Nordisk Ltd)
6057	Lantus 100iu/ml Injection (Aventis Pharma)
4198	Humulin m3 100unit/ml M3 injection (Eli Lilly and Company Ltd)

2929	Mixtard 30 100iu/ml GE injection (Novo Nordisk Ltd)
322	Humalog 100units/ml solution for injection 1.5ml cartridges (Eli Lilly and Company Ltd)
6965	Levemir Penfill 100units/ml solution for injection 3ml cartridges (Novo Nordisk Ltd)
7318	Humalog 100units/ml solution for injection 3ml cartridges (Eli Lilly and Company Ltd)
1886	Insulatard 100iu/ml GE injection (Novo Nordisk Ltd)
1588	Actrapid 100iu/ml Injection (Novo Nordisk Ltd)
1591	U100 Insulin syringe 1ml
4760	Humulin i 100unit/ml Injection (Eli Lilly and Company Ltd)
2221	Mixtard 30 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
7231	Mixtard 30 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
7237	Lantus 100units/ml solution for injection 3ml pre-filled OptiSet pen (Sanofi)
5953	Insulin glargine 100iu/ml Injection
4715	Humalog mix 25 25/75 100units/ml Injection (Eli Lilly and Company Ltd)
5966	Mylife Clickfine hypodermic insulin needles for pre-filled / reusable pen injectors snap on 8mm/31gauge (Ypsomed Ltd)
1587	Monotard 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
5845	Mixtard 30 InnoLet 100units/ml suspension for injection 3ml pre-filled pen (Novo Nordisk Ltd)
10243	Humalog Mix25 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
14290	Insulatard Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
43489	BD Micro-Fine Ultra hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge (Becton, Dickinson UK Ltd)
10277	Humulin M3 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
5850	Mylife Clickfine hypodermic insulin needles for pre-filled / reusable pen injectors snap on 6mm/31gauge (Ypsomed Ltd)
1840	Humulin s 100unit/ml Injection (Eli Lilly and Company Ltd)
7393	Insulin glargine 100units/ml solution for injection 3ml cartridges
7400	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices
2459	Pork Mixtard 30 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
5121	BD Micro-Fine + hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12.7mm/29gauge (Becton, Dickinson UK Ltd)
5022	NovoFine hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/28gauge (Novo Nordisk Ltd)
1844	Ultratard 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
4093	Humulin M2 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
1805	Mixtard 30/70 100unit/ml Injection (Novo Nordisk Ltd)
6209	NovoRapid 100units/ml solution for injection 10ml vials (Novo Nordisk Ltd)
1806	Penmix 30/70 100iu/ml Penfill (Novo Nordisk Ltd)
1843	Pork Insulatard 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
14357	Humulin I 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
7203	Unifine Pentips hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (Owen Mumford Ltd)
5267	BD Micro-Fine + hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm needle 0.3mm/30gauge (Becton, Dickinson UK Ltd)
1839	INSULIN HUMULIN I (ISOPHANE) 100 I/U INJ
1595	Insulatard NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
9363	U100 Insulin syringe 0.5ml
5059	NovoPen 3 Classic hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 2-70 units (Novo Nordisk Ltd)
43991	Humulin M3 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
7164	Unifine Pentips hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge (Owen Mumford Ltd)
10225	Lantus 100units/ml solution for injection 3ml OptiClik cartridges (Sanofi)

3551	Mixtard 20 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
39006	Humalog Mix25 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
14944	Humulin S 100units/ml solution for injection 3ml cartridges (Eli Lilly and Company Ltd)
10208	Insulatard InnoLet 100units/ml suspension for injection 3ml pre-filled pen (Novo Nordisk Ltd)
1594	Actrapid NovoLet 100units/ml solution for injection (Novo Nordisk Ltd)
7300	Mixtard 30 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
38986	Humalog KwikPen 100units/ml solution for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
1751	Hypodermic U100 insulin syringe glass reusable 1ml
4790	Mixtard 50 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
14270	Humalog Mix25 Pen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
7402	Lantus 100units/ml solution for injection 10ml vials (Sanofi)
5789	Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm needle 0.3mm/30gauge
36920	Apidra 100units/ml solution for injection 3ml pre-filled SoloStar pen (Sanofi)
14928	Insulatard 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
35143	NovoFine Autocover hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/30gauge (Novo Nordisk Ltd)
18593	Humalog Mix50 100units/ml suspension for injection 3ml cartridges (Eli Lilly and Company Ltd)
7793	HumaJect M3 Pen 100units/ml suspension for injection (Eli Lilly and Company Ltd)
6991	BD Micro-Fine + hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12.7mm needle 0.33mm/29gauge (Becton, Dickinson UK Ltd)
10264	Humalog Pen 100units/ml solution for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
10001	Humalog Mix50 Pen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
9702	BD Micro-Fine + hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12.7mm needle 0.33mm/29gauge (Becton, Dickinson UK Ltd)
39086	Humalog Mix50 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
7771	Human protaphane penfill 100 100unit/ml Penfill (Novo Nordisk Ltd)
6228	BD Micro-Fine + hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 8mm needle 0.3mm/30gauge (Becton, Dickinson UK Ltd)
7772	Human protaphane 100unit/ml Injection (Novo Nordisk Ltd)
18224	Humalog 100units/ml solution for injection 10ml vials (Eli Lilly and Company Ltd)
7349	Actrapid 100units/ml solution for injection 10ml vials (Novo Nordisk Ltd)
3550	Mixtard 40 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
1842	Pork velosulin 100unit/ml Injection (Novo Nordisk Ltd)
5742	Unifine Pentips hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/30gauge (Owen Mumford Ltd)
12297	Hypurin bovine neutral 100unit/ml Injection (C P Pharmaceuticals Ltd)
19513	Humulin M3 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
5255	Mixtard 10 penfill 100 100iu/ml Penfill (Novo Nordisk Ltd)
14330	Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices
10259	Insulin glargine 100units/ml solution for injection 10ml vials
14301	Insulin detemir 100units/ml solution for injection 3ml cartridges
1649	Human actraphane 100iu/ml Injection (Novo Nordisk Ltd)
5214	Insulin lispro 100units/ml solution for injection 1.5ml cartridges
6470	Autopen 24 hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units (Owen Mumford Ltd)
2373	INSULIN HUMAN VELOSULIN 100 I/U INJ
43950	Humulin I KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
9737	Insulatard innolet 100iu/ml Injection (Novo Nordisk Ltd)

13516	Hypurin bovine isophane 100unit/ml Injection (C P Pharmaceuticals Ltd)
10145	Humapen luxura insulin pen 3ml/1-60 units Insulin pen 3ml/1-60 units (Eli Lilly and Company Ltd)
8895	Initard 50/50 100unit/ml Injection (Novo Nordisk Ltd)
6378	Hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 8mm needle 0.3mm/30gauge
5933	Mixtard 50 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
7861	INSULIN HUMULIN S (NEUTRAL) CARTRIDGE 100 I/U
9521	Pork Actrapid 100units/ml solution for injection 10ml vials (Novo Nordisk Ltd)
7537	Humulin Zn 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
5967	Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with not less than 12mm needle 0.33mm/29gauge
11056	Insulin biphasic isophane human pyr 30:70; 100 units/ml Injection
2321	Insulin 0.5ml disposable syringe
38774	NovoPen 4 hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Blue (Novo Nordisk Ltd)
9578	Unifine Pentips hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge (Owen Mumford Ltd)
4199	Humulin m1 100unit/ml M1 injection (Eli Lilly and Company Ltd)
4706	Velosulin 100units/ml solution for injection 10ml vials (Novo Nordisk Ltd)
14918	Humulin I 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
7127	BD Micro-Fine + hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 8mm needle 0.3mm/30gauge (Becton, Dickinson UK Ltd)
2455	Mixtard 20 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
10184	Insulin detemir 100 iu/ml Solution for injection
6730	Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with not less than 12mm needle 0.33mm/29gauge
5891	Insulatard FlexPen 100units/ml suspension for injection (Novo Nordisk Ltd)
6138	HumaPen Ergo hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Burgundy (Eli Lilly and Company Ltd)
8841	Humulin M5 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
38808	NovoPen 4 hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Silver (Novo Nordisk Ltd)
13622	Hypurin porcine neutral 100unit/ml Injection (C P Pharmaceuticals Ltd)
11086	B-d u-100 0.5ml Insulin syringe (Becton, Dickinson UK Ltd)
35260	Levemir InnoLet 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
25786	Comfort Point hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge (Exel Int. (Europe) Ltd)
11080	Insulin isophane human prb 100iu/ml Injection
6724	U100 Insulin syringe 0.3ml
14313	Insulin lispro 100units/ml solution for injection 3ml cartridges
35454	Comfort Point hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (Exel Int. (Europe) Ltd)
10175	Insulin isophane human 100units/ml suspension for injection 1.5ml cartridges
6447	Insulin aspart human pyr 100 iu/ml Injection
2812	Mixtard 40 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
2456	Mixtard 10 NovoLet 100units/ml suspension for injection (Novo Nordisk Ltd)
16160	Humulin M3 Pen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
10258	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge
3076	NovoFine hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/30gauge (Novo Nordisk Ltd)
6781	Autopen Classic hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units (Owen Mumford Ltd)
5345	Monoject hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.36mm/28gauge (Covidien (UK) Commercial Ltd)

5164	NovoPen 3 Demi hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units (Novo Nordisk Ltd)
10242	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge
17712	Hypurin Bovine Lente 100units/ml suspension for injection 10ml vials (Wockhardt UK Ltd)
14345	Apidra 100units/ml solution for injection 3ml cartridges (Sanofi)
21235	Humulin S 100units/ml solution for injection 10ml vials (Eli Lilly and Company Ltd)
10229	Humulin I Pen 100units/ml suspension for injection 3ml pre-filled pen (Eli Lilly and Company Ltd)
13819	Hypurin Porcine Isophane 100units/ml suspension for injection 1.5ml cartridges (C P Pharmaceuticals Ltd)
6554	Autopen 24 hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units (Owen Mumford Ltd)
9341	Insulin biphasic isophane human prb 30:70; 100 units/ml Injection
7412	U100 Insulin syringe 0.5ml
16142	Insulin aspart 100units/ml solution for injection 3ml cartridges
14887	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge
11337	NovoRapid Novolet 100units/ml solution for injection (Novo Nordisk Ltd)
10546	INSULIN HUMULIN M4 100 I/U INJ
14930	Hypurin Porcine Neutral 100units/ml solution for injection 3ml cartridges (Wockhardt UK Ltd)
45045	NovoTwist hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/32gauge (Novo Nordisk Ltd)
9618	Hypurin Porcine 30/70 Mix 100units/ml suspension for injection 1.5ml cartridges (C P Pharmaceuticals Ltd)
20995	Hypurin Porcine 30/70 Mix 100units/ml suspension for injection 3ml cartridges (Wockhardt UK Ltd)
28183	Hypurin Porcine Isophane 100units/ml suspension for injection 10ml vials (Wockhardt UK Ltd)
4896	Monoject hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.36mm/28gauge (Covidien (UK) Commercial Ltd)
6060	Unifine Pentips hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/30gauge (Owen Mumford Ltd)
13009	Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.36mm/28gauge
58745	GlucoRx FinePoint hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/31gauge (GlucoRx Ltd)
26098	Hypurin Porcine Neutral 100units/ml solution for injection 10ml vials (Wockhardt UK Ltd)
33966	Insulatard 100unit/ml Injection (Novo Nordisk Ltd)
15199	Insuman comb 25 100iu/ml Injection (Aventis Pharma)
11107	Humulin m4 100unit/ml M4 injection (Eli Lilly and Company Ltd)
5557	NovoPen 3 Fun hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 2-70 units Blue (Novo Nordisk Ltd)
7075	Optipen Pro 1 hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units (Sanofi)
11271	B-d u-100 1ml Insulin syringe (Becton, Dickinson UK Ltd)
24800	Hypurin Porcine 30/70 Mix 100units/ml suspension for injection 10ml vials (Wockhardt UK Ltd)
8118	Humaject i 100iu/ml Pen (Eli Lilly and Company Ltd)
4784	Lentard mc 100unit/ml Injection (Novo Nordisk Ltd)
13277	Mixtard 50 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
14642	Bd m 0.3ml Insulin syringe with 29gauge needle 12mm (Becton, Dickinson UK Ltd)
9565	HumaJect S Pen 100units/ml solution for injection (Eli Lilly and Company Ltd)
7783	INSULIN ISOPHANE (HUMAN) 100 I/U INJ
7319	Mixtard 20 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
6233	Mylife Clickfine hypodermic insulin needles for pre-filled / reusable pen injectors snap on 10mm/29gauge (Ypsomed Ltd)
11878	Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 8mm needle 0.3mm/30gauge
6091	NovoPen 3 Fun hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 2-70 units Red (Novo Nordisk Ltd)

8203	Penmix 50/50 100iu/ml Penfill (Novo Nordisk Ltd)
5250	Insulin biphasic lispro human prb 25:75; 100 units/ml Injection
4247	Insulin isophane porcine 100units/ml suspension for injection 1.5ml cartridges
19271	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/30gauge
12840	B-d u-100 0.5ml Insulin syringe (Becton, Dickinson UK Ltd)
12638	Insulin soluble human pyr 100unit/ml Injection
10545	INSULIN HUMULIN M4 CARTRIDGE 100 I/U
44480	Insuman Comb 25 100units/ml suspension for injection 3ml pre-filled SoloStar pen (Sanofi)
5634	Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.36mm/28gauge
10484	Penmix 20/80 Penfill (Novo Nordisk Ltd)
22060	Insulin 0.5 0.5ml Syringe
6831	HumaPen Ergo hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Teal (Eli Lilly and Company Ltd)
9834	Mylife Clickfine hypodermic insulin needles for pre-filled / reusable pen injectors snap on 12mm/29gauge (Ypsomed Ltd)
48633	Comfort Point hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/31gauge (Exel Int. (Europe) Ltd)
19877	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices
10547	Humulin Lente 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
58884	GlucoRx FinePoint hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (GlucoRx Ltd)
10067	Insulin biphasic aspart human pyr 30:70; 100 units/ml Injection
14933	Hypurin Porcine Isophane 100units/ml suspension for injection 3ml cartridges (Wockhardt UK Ltd)
58798	GlucoRx FinePoint hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge (GlucoRx Ltd)
12818	Human Mixtard 50 100units/ml suspension for injection 10ml vials (Novo Nordisk Ltd)
10572	Insulin soluble bovine 100unit/ml Injection
11346	B-d u-100 0.3ml Insulin syringe (Becton, Dickinson UK Ltd)
24993	Insuman Comb 25 100units/ml suspension for injection 3ml cartridges (Sanofi)
58961	Mylife Penfine Classic hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge (Ypsomed Ltd)
14339	Hypurin Bovine Neutral 100units/ml solution for injection 10ml vials (Wockhardt UK Ltd)
4163	Rapitard MC 100unit/ml Injection (Novo Nordisk Ltd)
23636	Insulin 1ml disposable syringe
10133	U100 Insulin syringe 1ml
25133	Insuman Comb 25 100units/ml suspension for injection 3ml pre-filled OptiSet pen (Sanofi)
19491	Apidra 100units/ml solution for injection 10ml vials (Sanofi)
23099	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
43833	ClikSTAR hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units Blue (Sanofi)
6753	Novopen Junior hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units Green (Novo Nordisk Ltd)
12299	Semitard mc 100unit/ml Injection (Novo Nordisk Ltd)
4129	Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges
11408	Autopen Classic hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units (Owen Mumford Ltd)
14340	Hypurin Bovine Isophane 100units/ml suspension for injection 10ml vials (Wockhardt UK Ltd)
14362	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices
10887	Penmix 40/60 100iu/ml Penfill (Novo Nordisk Ltd)
14619	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 1.5ml cartridges
48342	HumaPen Luxura hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Burgundy (Eli Lilly and Company Ltd)

10910	Humaject m2 100iu/ml M2 pen (Eli Lilly and Company Ltd)
46666	NovoRapid FlexTouch 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
5620	U100 Insulin syringe 0.3ml
21583	Apidra 100units/ml solution for injection 3ml pre-filled OptiSet pen (Sanofi)
10244	Mixtard 40 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
10245	Mixtard 10 Penfill 100units/ml suspension for injection 3ml cartridges (Novo Nordisk Ltd)
48765	Unifine Pentips hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge (Owen Mumford Ltd)
43670	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge
17809	Humaject m4 100iu/ml M4 pen (Eli Lilly and Company Ltd)
46001	Insuman Basal 100units/ml suspension for injection 3ml pre-filled SoloStar pen (Sanofi)
15484	Insulin isophane bovine 100units/ml suspension for injection 1.5ml cartridges
48435	BD AutoShield hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/29gauge (Becton, Dickinson UK Ltd)
12654	Insulin soluble human prb 100unit/ml Injection
35078	Optipen pro 1 blue insulin pen 3ml/1-60 units 3ml/1-60 units Insulin pen (Aventis Pharma)
27461	Insuman Basal 100units/ml suspension for injection 3ml cartridges (Sanofi)
59005	Mylife Penfine Classic hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (Ypsomed Ltd)
16152	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges
8376	INSULIN ISOPHANE 100 I/U
35253	Insuman Comb 50 100units/ml suspension for injection 3ml cartridges (Sanofi)
5769	Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.4mm/27gauge
37427	HumaPen Luxura HD hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units (Eli Lilly and Company Ltd)
27614	Penmix 30/70 100iu/ml Injection (Novo Nordisk Ltd)
5501	Insuman basal 100iu/ml Injection (Aventis Pharma)
26060	Insulin lispro 100units/ml solution for injection 10ml vials
9079	INSULIN SOLUBLE 100 I/U INJ
29953	Apidra 100units/ml solution for injection 3ml OptiClik cartridges (Sanofi)
14504	INSULIN HYPURIN PROTAMINE ZINC 100 I/U INJ
35057	OptiClik hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units Blue (Sanofi)
2808	INSULIN LENTARD INJ
11055	Insulin biphasic isophane human pyr 20:80; 100 units/ml Injection
22974	Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 8mm/31gauge
11245	B-d u-100 0.3ml Insulin syringe (Becton, Dickinson UK Ltd)
9503	Hypurin Bovine Protamine Zinc 100units/ml suspension for injection 10ml vials (Wockhardt UK Ltd)
6981	Novopen Junior hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units Yellow (Novo Nordisk Ltd)
34713	Insulin 1 ml syringe
2220	Penmix 20/80 Pen (Novo Nordisk Ltd)
17731	Penmix 50/50 100iu/ml Injection (Novo Nordisk Ltd)
14646	Hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 12mm needle 0.33mm/29gauge
12892	Clinipak u100 single use ins syr+12mm need28g 0.5ml [rand] 0.5ml Insulin syringe with 28gauge needle 12mm (Rand Rocket Ltd)
3396	Penmix 10/90 Penfill (Novo Nordisk Ltd)
59004	Mylife Penfine Classic hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/32gauge (Ypsomed Ltd)
24795	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges

48501	HumaPen Luxura hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Champagne (Eli Lilly and Company Ltd)
11521	Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.4mm/27gauge
10915	Humaject m1 100iu/ml M1 pen (Eli Lilly and Company Ltd)
22983	Insuman Rapid 100units/ml solution for injection 3ml cartridges (Sanofi)
28185	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges
21347	Penmix 40/60 100iu/ml Injection (Novo Nordisk Ltd)
10207	Insulin isophane human 100units/ml suspension for injection 3ml cartridges
11345	Bd Ultra Pen 3ml Insulin pen (Becton, Dickinson UK Ltd)
30819	Insuman Comb 15 100units/ml suspension for injection 3ml pre-filled OptiSet pen (Sanofi)
43568	ClikSTAR hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units Silver (Sanofi)
22697	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges
14644	Insulin biphasic isophane human prb 20:80; 100 units/ml Injection
18195	Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 6mm/31gauge
15294	Innovo hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-70 units Green (Novo Nordisk Ltd)
42395	Humalog Mix25 100units/ml suspension for injection 10ml vials (Eli Lilly and Company Ltd)
20672	INSULIN HUM/ACTRAPID
23231	Hypurin Bovine Neutral 100units/ml solution for injection 3ml cartridges (Wockhardt UK Ltd)
18149	Monoject u100 insulin syringe 12mm(29g)0.5ml 12mm29G 0.5ml Insulin syringe (Covidien (UK) Commercial Ltd)
14505	Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials
48829	NovoPen Echo hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 0.5-30 units Blue (Novo Nordisk Ltd)
10566	INSULIN HUMULIN M CARTRIDGE 100 I/U
29567	Insulin aspart 100units/ml solution for injection 10ml vials
8322	Insulin zinc suspension mixed human pyr 100unit/ml Injection
14299	Insulin glulisine 100units/ml solution for injection 3ml cartridges
8483	MONOJECT INSULIN NEEDLES
22945	Insuman rapid 100iu/ml Injection (Aventis Pharma)
21395	Insulin biphasic isophane human pyr 40:60; 100 units/ml Injection
8839	INSULIN SEMITARD 100 I/U INJ
28588	Hypurin Bovine Isophane 100units/ml suspension for injection 3ml cartridges (Wockhardt UK Ltd)
21590	Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices
31258	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
4248	INSULIN NOVO ULTRATARD MC 100 I/U INJ
8838	INSULIN SEMITARD 40 I/U INJ
21554	Insuman comb 50 100iu/ml Injection (Aventis Pharma)
1645	INSULIN NOVO ACTRAPID MC 100 I/U INJ
21232	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials
13096	Autopen hypodermic insulin injection pen reusable for 1.5ml cartridge 2 unit dial up / range 2-32 units (Owen Mumford Ltd)
15895	Innovo hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-70 units Orange (Novo Nordisk Ltd)
14649	Insulin biphasic isophane human pyr 10:90; 100 units/ml Injection
36959	Comfort Point hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge (Exel Int. (Europe) Ltd)
12035	Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials
1643	INSULIN NOVO MONOTARD MC 100 I/U INJ
28101	Insulin glulisine 100units/ml solution for injection 10ml vials

321	INSULIN HUMAN ACTRAPID (NEUTRAL) 40 I/U INJ
8354	INSULIN ISOPHANE 70%/NEUTRAL 30% 100 I/U INJ
12300	SYRINGE INSULIN (BS1619/1) 2ML
7765	INSULIN NEUTRAL (HUMAN) 100 I/U INJ
49172	NovoPen Echo hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 0.5-30 units Red (Novo Nordisk Ltd)
5649	Autopen hypodermic insulin injection pen reusable for 1.5ml cartridge 1 unit dial up / range 1-16 units (Owen Mumford Ltd)
31205	Insuman Comb 50 100units/ml suspension for injection 3ml pre-filled OptiSet pen (Sanofi)
51650	Omnican Fine hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge (B.Braun Medical Ltd)
21945	INSULIN PORK INSULATARD
13837	Insulin biphasic isophane human prb 10:90; 100 units/ml Injection
24002	Insuman Comb 25 100units/ml suspension for injection 5ml vials (Sanofi)
13729	Insulin isophane human emp 100unit/ml Injection
13416	Insulin biphasic 100 units/ml Injection
23992	Insuman Basal 100units/ml suspension for injection 3ml pre-filled OptiSet pen (Sanofi)
27280	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials
15710	Insulin soluble human emp 100unit/ml Injection
14925	Insulin isophane human vial 100unit/ml Sterile suspension injection
48811	Unifine Pentips Plus hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge (Owen Mumford Ltd)
13474	U100 Insulin syringe Sp.36 [2A] 1ml
23993	Insuman Rapid 100units/ml solution for injection 3ml pre-filled OptiSet pen (Sanofi)
13036	Unifine hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.33mm/29gauge (Owen Mumford Ltd)
18446	Unifine hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.33mm/29gauge (Owen Mumford Ltd)
9376	Insulin zinc suspension crystalline human pyr 100unit/ml long acting Injection
3439	Penmix 10/90 Pen (Novo Nordisk Ltd)
13274	Clinipak u100 single use ins syr+12mm need28g 1ml [rand] 1ml Insulin syringe with 28gauge needle 12mm (Rand Rocket Ltd)
16129	Insulin soluble human 100units/ml solution for injection 3ml cartridges
45158	Insuman Comb 15 100units/ml suspension for injection 3ml cartridges (Sanofi)
15961	Insulin isophane human crb 100iu/ml Injection
7764	INSULIN NEUSULIN (NEUTRAL)(PURIFIED) 100 I/U INJ
19878	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices
21374	Insulin biphasic isophane human prb 40:60; 100 units/ml Injection
30209	Actrapid mc 100unit/ml Injection (Arun Products Ltd)
25812	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices
40555	HumaPen Memoir hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units (Eli Lilly and Company Ltd)
13969	U100 Insulin syringe 0.3ml
36513	Velosulin cartridge 100unit/ml Injection (Novo Nordisk Ltd)
30236	Isophane insulin 100iu/ml Injection
39150	Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm safety needle 0.33mm/29gauge
49307	Mylife Clickfine hypodermic insulin needles for pre-filled / reusable pen injectors snap on 4.5mm/31gauge (Ypsomed Ltd)
9619	Bd Ultra Pen 1.5ml Insulin pen (Becton, Dickinson UK Ltd)
59846	Mylife Clickfine hypodermic insulin needles for pre-filled / reusable pen injectors snap on 4mm/32gauge (Ypsomed Ltd)
34097	Human initard 50/50 100unit/ml Injection (Novo Nordisk Ltd)

7763	INSULIN NEUPHANE (ISOPHANE)(PURIFIED) 100 I/U INJ
17643	Autopen Special Edition hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units (Owen Mumford Ltd)
14506	INSULIN BOVINE PROTAMINE ZINC 100 I/U INJ
49479	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/31gauge
24722	INSULIN ISOPHANE 50%/NEUTRAL 50% 100 I/U INJ
33101	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12.7mm/29gauge
7757	INSULIN NEULENTE (ZINC SUSP)(PURIFIED) 100 I/U INJ
35081	OptiClik hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units Grey (Sanofi)
27177	Insulin biphasic lispro human prb 50:50; 100 units/ml Injection
49451	Mylife Clickfine AutoProtect hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/29gauge (Ypsomed Ltd)
21223	U100 Insulin syringe 0.3ml
55462	Tresiba FlexTouch 100units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
15951	Autopen Junior hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units (Owen Mumford Ltd)
26403	Pur-in mix 25/75 Injection (C P Pharmaceuticals Ltd)
13550	INSULIN BP 100 I/U
49052	Unifine Pentips Plus hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (Owen Mumford Ltd)
20422	Insuman comb 15 100iu/ml Injection (Aventis Pharma)
24846	Pur-in neutral 100unit/ml Injection (C P Pharmaceuticals Ltd)
15624	INSULIN ISOPHANE (HIGHLY PURIFIED) 100 I/U INJ
10691	INSULIN ISOPHANE (NPH) 100 I/U INJ
14191	Autopen Junior hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units (Owen Mumford Ltd)
16866	Unifine hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 12mm needle 0.33mm/29gauge (Owen Mumford Ltd)
56495	Lantus 100units/ml solution for injection 3ml pre-filled OptiSet pen (Waymade Healthcare Plc)
12060	INSULIN QUICKSOL (SOLUBLE NEUTRAL) 100 I/U INJ
35218	Optipen pro 1 yellow insulin pen 3ml/1-60 units 3ml/1-60 units Insulin pen (Aventis Pharma)
27402	Insulin soluble human 100units/ml solution for injection 10ml vials
48771	Unifine Pentips Plus hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge (Owen Mumford Ltd)
51881	Omnican Fine hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (B.Braun Medical Ltd)
48576	BD AutoShield Duo hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/30gauge (Becton, Dickinson UK Ltd)
24845	INSULIN PUR-IN ISOPHANE 100 I/U INJ
24593	Neutral insulin bovine 100unit/ml Injection
7062	Myjector hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.4mm/27gauge (Terumo UK Ltd)
35017	Optipen pro 1 white insulin pen 3ml/1-60 units 3ml/1-60 units Insulin pen (Aventis Pharma)
7350	Insulin isophane porcine 100units/ml suspension for injection 10ml vials
22328	Unifine single use Insulin syringe with 30gauge needle 8mm 0.5ml (Owen Mumford Ltd)
38093	Insulin 1ml pre-set syringe
18931	Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials
25422	Hypoguard u100 click/count 1ml Insulin syringe (Hypoguard Ltd)
44810	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/32gauge
8646	INSULIN ZINC CRYSTALLINE susp 100 I/U INJ
23437	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/28gauge
16959	Hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.3mm/30gauge

35701	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
6009	Myjector hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.4mm/27gauge (Terumo UK Ltd)
34031	Monotard mc 100unit/ml Injection (Novo Nordisk Ltd)
13108	Autopen Special Edition hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units (Owen Mumford Ltd)
18590	Insulin isophane bovine 100units/ml suspension for injection 10ml vials
31465	Exubera 1mg inhalation powder blisters (Pfizer Ltd)
58817	GlucoRx FinePoint hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge (GlucoRx Ltd)
17076	Omnican 100 hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 8mm needle 0.3mm/30gauge (B.Braun Medical Ltd)
18645	INSULIN NEUTRAL (PURIFIED) 100 I/U INJ
55234	Tresiba FlexTouch 200units/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
31467	Exubera 3mg inhalation powder blisters (Pfizer Ltd)
16389	Myjector hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.33mm/29gauge (Terumo UK Ltd)
57529	Humalog 100units/ml solution for injection 10ml vials (Dowelhurst Ltd)
35468	Insuman Basal 100units/ml suspension for injection 5ml vials (Sanofi)
21110	Insulin biphasic isophane human prb 50:50; 100 units/ml Injection
25479	Insulin soluble porcine 100units/ml solution for injection 3ml cartridges
36031	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges
56489	NovoMix 30 Penfill 100units/ml suspension for injection 3ml cartridges (Waymade Healthcare Plc)
16209	INSULIN HYPURIN SOLUBLE 100 I/U INJ
20671	INSULIN HUM/ACTRAPHANE
30686	Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges
33356	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge
58801	GlucoRx FinePoint hypodermic insulin needles for pre-filled / reusable pen injectors screw on 10mm/29gauge (GlucoRx Ltd)
59475	Nanopass hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32.5gauge (Terumo UK Ltd)
18592	Insulin soluble bovine 100units/ml solution for injection 10ml vials
24866	INSULIN INSULATARD (LEO RETARD) 40 I/U INJ
28666	Omnican 50 hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm needle 0.3mm/30gauge (B.Braun Medical Ltd)
17336	Novopen 100unit/ml Injection device (Novo Nordisk Ltd)
47751	TS-A Safety hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm safety needle 0.33mm/29gauge (Minsmed)
15040	INSULIN MONOPHANE (ISOPHANE) 100 I/U INJ
28723	INSULIN ZINC BOVINE SUSPENSION
61845	NovoRapid PumpCart 100units/ml solution for injection 1.6ml cartridges (Novo Nordisk Ltd)
56502	Actrapid Penfill 100units/ml solution for injection 3ml cartridges (Novo Nordisk Ltd)
36146	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges
22496	INSULIN ZINC LENTE PURIFIED SUSPENSION
57564	Humalog KwikPen 100units/ml solution for injection 3ml pre-filled pen (Waymade Healthcare Plc)
21422	Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges
28442	Insulin glulisine 100unit/ml Solution for injection
22155	Humaject m5 100iu/ml M5 pen (Eli Lilly and Company Ltd)
26621	Insulin soluble human crb 100iu/ml Injection
28096	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges
31466	Exubera insulin release unit (Pfizer Ltd)
12244	INSULIN ZINC BOVINE susp 100 I/U INJ

18208	Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 10mm/29gauge
30305	Hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.3mm/30gauge
22094	INSULIN HUMULIN M2 VIAL
25736	Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges
37055	Comfort Point hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.33mm/29gauge (Exel Int. (Europe) Ltd)
51612	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/29gauge
56639	HumaPen Savvio hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Blue (Eli Lilly and Company Ltd)
19977	Omnican 50 hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm needle 0.3mm/30gauge (B.Braun Medical Ltd)
38422	Isophane 100iu/ml Injection (Celltech Pharma Europe Ltd)
55687	Insulin degludec 100units/ml solution for injection 3ml pre-filled disposable devices
18461	Insulin zinc mixed human 100units/ml suspension for injection 10ml vials
59793	Microdot Droplet hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge (Cambridge Sensors Ltd)
22946	Omnican 100 hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.3mm/30gauge (B.Braun Medical Ltd)
26338	Injex starter set 60500 (Ocon Chemicals Ltd)
30861	INSULIN ZINC HUMAN SUSPENSION
36356	Insulin human 3mg inhalation powder blisters
52748	Insulatard Penfill 100units/ml suspension for injection 3ml cartridges (Waymade Healthcare Plc)
24554	Unifine single use Insulin syringe with 30gauge needle 8mm 0.3ml (Owen Mumford Ltd)
26498	Insulin zinc suspension mixed bovine and porcine 100unit/ml Injection
53148	Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units
56691	Insulin degludec 200units/ml solution for injection 3ml pre-filled disposable devices
38236	Comfort Point hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm needle 0.33mm/29gauge (Exel Int. (Europe) Ltd)
55521	Insupen hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge (Spirit Healthcare Ltd)
56785	HumaPen Savvio hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Red (Eli Lilly and Company Ltd)
57744	Omnican Fine hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/31gauge (B.Braun Medical Ltd)
14938	Insulin soluble bovine cartridge 100unit/ml Solution for injection
36430	Insulin soluble human 100units/ml solution for injection 3ml pre-filled disposable devices
42797	Injex ampoule pack 60501 (Ocon Chemicals Ltd)
16700	Insulin zinc mixed bovine vial 100unit/ml Sterile suspension injection
18301	INSULIN SOLUBLE INJ I/U^2
49507	InsuJet nozzle pack 012070GB15 (Spirit Healthcare Ltd)
19707	INSULIN HUMULIN S (NEUTRAL SOLUBLE)
22161	INSULIN HUMULIN M1 VIAL
27396	Insulin soluble porcine 100units/ml solution for injection 10ml vials
42305	Injex 10ml vial adaptor pack 60502 (Ocon Chemicals Ltd)
50691	Human Mixtard 20 Penfill 100units/ml suspension for injection 1.5ml cartridges (Novo Nordisk Ltd)
55910	Tresiba Penfill 100units/ml solution for injection 3ml cartridges (Novo Nordisk Ltd)
56879	HumaPen Savvio hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Graphite (Eli Lilly and Company Ltd)
52722	Human Mixtard 30 Penfill 100units/ml suspension for injection 1.5ml cartridges (Novo Nordisk Ltd)
19029	SYRINGE PRE-SET INSULIN FOR BLIND 2ML
30918	ABCare hypodermic U100 insulin syringe glass reusable 0.5ml (Rand Rocket Ltd)
36355	Insulin human 1mg inhalation powder blisters

41834	Insulin zinc suspension lente 100iu/ml Injection (Celltech Pharma Europe Ltd)
49508	InsuJet 10ml vial adaptor pack 01207GB1510 (Spirit Healthcare Ltd)
56642	Microdot Droplet hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge (Cambridge Sensors Ltd)
56808	Omnican Fine hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge (B.Braun Medical Ltd)
57153	Kendall Magellan hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm safety needle 0.3mm/30gauge (Covidien (UK) Commercial Ltd)
59243	BD SafetyGlide hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 8mm safety needle 0.25mm/31gauge (Becton, Dickinson UK Ltd)
60967	Nanopass hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/32.5gauge (Terumo UK Ltd)
22987	Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 12mm/29gauge
43953	Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials
47360	Neutral insulin 100unit/ml Injection (Celltech Pharma Europe Ltd)
56656	Kendall Magellan hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 8mm safety needle 0.3mm/30gauge (Covidien (UK) Commercial Ltd)
58754	BD SafetyGlide hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm safety needle 0.33mm/29gauge (Becton, Dickinson UK Ltd)
32053	INSULIN HUMALOG MIX 25
55907	Insulin degludec 100units/ml solution for injection 3ml cartridges
57493	HumaPen Savvio hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Silver (Eli Lilly and Company Ltd)
60028	Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 4mm/32gauge
60750	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/33gauge
56352	HumaPen Savvio hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Green (Eli Lilly and Company Ltd)
56939	HumaPen Savvio hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-60 units Pink (Eli Lilly and Company Ltd)
57388	Kendall Magellan hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 8mm safety needle 0.3mm/30gauge (Covidien (UK) Commercial Ltd)
58449	Unifine Pentips hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32gauge (Owen Mumford Ltd)
25735	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges
54028	Unifine Pentips Plus hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge (Owen Mumford Ltd)
56115	Human Actrapid Penfill 100units/ml solution for injection 1.5ml cartridges (Novo Nordisk Ltd)
58995	BD SafetyGlide hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm safety needle 0.33mm/29gauge (Becton, Dickinson UK Ltd)
16682	Tempulin 100unit/ml Injection (Knoll Ltd)
19829	INSULIN NOVO MONOTARD MC
33167	Insulin biphasic isophane human crb 25:75; 100 units/ml Injection
55517	Insulin isophane human 100units/ml suspension for injection 10ml vials
60938	Mixtard 30 100units/ml suspension for injection 10ml vials (Waymade Healthcare Plc)
22823	INSULIN ISOPHANE (PURIFIED) 100 I/U INJ
24485	INSULIN ZINC ANIMAL SUSPENSION
27151	SYRINGE INSULIN U100 S/U+8MM NEEDLE
44378	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices
44601	Injex 4 monthly refill pack 60504 (Ocon Chemicals Ltd)
54027	Hypodermic insulin needles for pre-filled / reusable pen injectors snap on 4.5mm/31gauge
54885	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/32gauge
57622	Humalog Mix50 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Waymade Healthcare Plc)
36066	Insulin isophane bovine 100units/ml suspension for injection 3ml cartridges
42954	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials

49831	Lantus 100units/ml solution for injection 3ml pre-filled SoloStar pen (Necessity Supplies Ltd)
55627	Insupen hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge (Spirit Healthcare Ltd)
41959	Penject 100unit/ml Injection device (Hypoguard Ltd)
57620	Humulin M3 100units/ml suspension for injection 10ml vials (Mawdsley-Brooks & Company Ltd)
60933	Humulin M3 100units/ml suspension for injection 10ml vials (Sigma Pharmaceuticals Plc)
28978	INSULIN PUR-IN MIX 15/85 100 I/U INJ
40085	Insulin 2ml syringe
47588	Insulin 1ml click count
49509	InsuJet starter set 012005GBSP Blue (Spirit Healthcare Ltd)
56624	Kendall Magellan hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm safety needle 0.3mm/30gauge (Covidien (UK) Commercial Ltd)
49506	Insujet needle free starter kit Starter kit (European Pharma Group BV)
59133	BD SafetyGlide hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 8mm safety needle 0.3mm/30gauge (Becton, Dickinson UK Ltd)
59311	Kendall Magellan hypodermic U100 insulin syringe sterile single use / single patient use 1ml with 12mm safety needle 0.33mm/29gauge (Covidien (UK) Commercial Ltd)
31699	ABCare hypodermic U100 insulin syringe glass reusable 1ml (Rand Rocket Ltd)
41120	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices
52319	Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-80 units
54886	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/32gauge
55746	Insupen hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/32gauge (Spirit Healthcare Ltd)
56983	Insupen hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge (Spirit Healthcare Ltd)
57451	Microdot Droplet hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (Cambridge Sensors Ltd)
60609	Insupen hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/32gauge (Spirit Healthcare Ltd)
20195	INSULIN BOVINE PROTAMINE ZINC 40 I/U INJ
20196	INSULIN SOLUBLE 40 I/U INJ
21459	SYRINGE INSULIN U100 S/U+8MM NEEDLE
47856	Neuphane 100unit/ml Injection (Wellcome Medical Division)
50633	Lantus 100units/ml solution for injection 3ml cartridges (Necessity Supplies Ltd)
51107	Hypodermic insulin injection pen reusable for 3ml cartridge 2 unit dial up / range 2-42 units
51182	InsuJet starter set 012003GBSP Lime (Spirit Healthcare Ltd)
53118	NovoRapid FlexPen 100units/ml solution for injection 3ml pre-filled pen (Mawdsley-Brooks & Company Ltd)
56857	Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml cartridges
57387	Kendall Magellan hypodermic U100 insulin syringe sterile single use / single patient use 0.3ml with 12mm safety needle 0.33mm/29gauge (Covidien (UK) Commercial Ltd)
60621	Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 0.5-30 units
36194	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges
50798	Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-35 units
52232	Hypodermic insulin injection pen reusable for 3ml cartridge 0.5 unit dial up / range 1-30 units
58878	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 10mm/29gauge
61562	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/29gauge
26784	INSULIN ZINC SEMILENTE SUSP BP 100 I/U INJ
29837	Insulin biphasic isophane human prb 25:75; 100 units/ml Injection
31267	INSULIN PUR-IN MIX 50/50 100 I/U INJ
45639	IME-FINE hypodermic insulin needles for pre-filled / reusable pen injectors screw on 6mm/31gauge (Arctic Medical Ltd)
49108	NovoRapid Penfill 100units/ml solution for injection 3ml cartridges (Necessity Supplies Ltd)

51836	InsuJet 3ml cartridge adaptor pack 012071GB1503 (Spirit Healthcare Ltd)
53437	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/30gauge
53710	Insulin human 500units/ml solution for injection 20ml vials
54573	Hypodermic insulin injection pen reusable for 3ml cartridge 1 unit dial up / range 1-21 units
58579	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 4mm/32.5gauge
61780	Insupen hypodermic insulin needles for pre-filled / reusable pen injectors screw on 12mm/29gauge (Spirit Healthcare Ltd)
7959	INSULIN MIXTARD 30/70 40 I/U INJ
22806	INSULIN PORK ACTRAPID
23003	INSULIN ISOPHANE (NPH) 40 I/U
25006	INSULIN HUMAN ACTRAPID (NEUTRAL)
26795	SYRINGE INSULIN DISPOSABLE
27911	INSULIN HUMAN ACTRAPID PENFILL
33232	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 5ml vials
44251	Insulin zinc suspension mixed porcine 100unit/ml Injection
51743	NovoRapid Penfill 100units/ml solution for injection 3ml cartridges (Sigma Pharmaceuticals Plc)
52522	Humalog Mix50 KwikPen 100units/ml suspension for injection 3ml pre-filled pen (Doncaster Pharmaceuticals Ltd)
53251	NovoRapid Penfill 100units/ml solution for injection 3ml cartridges (Doncaster Pharmaceuticals Ltd)
54462	Insulin biphasic isophane human emp 25:75; 100 units/ml Injection
54629	Insupen hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/31gauge (Spirit Healthcare Ltd)
55603	Humalog KwikPen 100units/ml solution for injection 3ml pre-filled pen (Doncaster Pharmaceuticals Ltd)
55618	Levemir FlexPen 100units/ml solution for injection 3ml pre-filled pen (Waymade Healthcare Plc)
57243	Omnican Fine hypodermic insulin needles for pre-filled / reusable pen injectors screw on 10mm/30gauge (B.Braun Medical Ltd)
58578	Kendall Magellan hypodermic U100 insulin syringe sterile single use / single patient use 0.5ml with 12mm safety needle 0.33mm/29gauge (Covidien (UK) Commercial Ltd)
58581	GlucoRx FinePoint hypodermic insulin needles for pre-filled / reusable pen injectors screw on 5mm/31gauge (GlucoRx Ltd)
59500	Insulin isophane human 100units/ml suspension for injection 5ml vials
59533	NovoRapid FlexPen 100units/ml solution for injection 3ml pre-filled pen (Sigma Pharmaceuticals Plc)
60626	InsuJet starter set 012007GBSP Grey (Spirit Healthcare Ltd)
60951	Insulin human 100units/ml solution for injection 10ml vials
62098	Hypodermic insulin needles for pre-filled / reusable pen injectors screw on 8mm/32.5gauge
62180	Insulin aspart 100units/ml solution for injection 1.6ml cartridges
62276	Humulin R 500units/ml solution for injection 20ml vials (Imported (United States))
22058	Pur-in mix 15/85 Injection (C P Pharmaceuticals Ltd)
23	Metformin 500mg tablets
93	Metformin 850mg tablets
7048	Metformin 500mg modified-release tablets
39598	Metformin 1g modified-release tablets
16044	Glucophage SR 500mg tablets (Merck Serono Ltd)
7166	Glucophage 500mg tablets (Merck Serono Ltd)
38355	Metformin 750mg modified-release tablets
7610	Glucophage 850mg tablets (Merck Serono Ltd)
39729	Glucophage SR 1000mg tablets (Merck Serono Ltd)
39988	Metformin 500mg oral powder sachets sugar free
11990	Metformin 500mg/5ml oral solution sugar free
38400	Glucophage SR 750mg tablets (Merck Serono Ltd)

40233	Metformin 1g oral powder sachets sugar free
735	Metformin 100mg/ml Oral solution
25678	Glucamet 500mg Tablet (Opus Pharmaceuticals Ltd)
34917	Metformin 500mg tablets (Teva UK Ltd)
40110	Glucophage 500mg oral powder sachets (Merck Serono Ltd)
34323	Metformin 500mg tablets (A A H Pharmaceuticals Ltd)
3252	METFORMIN HCl 500 MG TAB
33087	Metformin 500mg tablets (Actavis UK Ltd)
40007	Glucophage 1000mg oral powder sachets (Merck Serono Ltd)
2928	METFORMIN HCl 850 MG TAB
34004	Metformin 500mg tablets (IVAX Pharmaceuticals UK Ltd)
26258	Glucamet 850mg Tablet (Opus Pharmaceuticals Ltd)
39560	Bolamyn SR 500mg tablets (Teva UK Ltd)
34742	Metformin 850mg tablets (Teva UK Ltd)
34020	Metformin 850mg tablets (IVAX Pharmaceuticals UK Ltd)
34598	Metformin 500mg tablets (Generics (UK) Ltd)
45581	Metabet SR 500mg tablets (Morningside Healthcare Ltd)
61559	Sukkarto SR 500mg tablets (Morningside Healthcare Ltd)
31146	Metsol 500mg/5ml oral solution (Kappin Ltd)
61043	Sukkarto SR 1000mg tablets (Morningside Healthcare Ltd)
33674	Metformin 850mg tablets (A A H Pharmaceuticals Ltd)
53774	Metabet SR 500mg tablets (Actavis UK Ltd)
34504	Metformin 500mg tablets (Wockhardt UK Ltd)
34697	Metformin 850mg tablets (Wockhardt UK Ltd)
58051	Metformin 500mg/5ml oral solution
7815	METFORMIN 800 MG TAB
57147	Bolamyn SR 1000mg tablets (Teva UK Ltd)
16213	METFORMIN 250 MG TAB
52221	Diagemet XL 500mg tablets (Genus Pharmaceuticals Ltd)
34836	Metformin 850mg tablets (Actavis UK Ltd)
46989	Metabet SR 1000mg tablets (Morningside Healthcare Ltd)
47939	Glucient SR 500mg tablets (Consilient Health Ltd)
51080	Metabet SR 1000mg tablets (Actavis UK Ltd)
60286	Metformin 500mg/5ml oral suspension
27501	Orabet 500mg Tablet (Lagap)
44250	Metformin 500mg/5ml Oral solution (Hillcross Pharmaceuticals Ltd)
55711	Metformin 500mg tablets (Alliance Healthcare (Distribution) Ltd)
42161	Orabet 500mg Tablet (Sandoz Ltd)
43270	Metformin 500mg/5ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)
20810	METFORMIN
34135	Metformin 500mg Tablet (M & A Pharmachem Ltd)
50570	Glucophage SR 500mg tablets (Lexon (UK) Ltd)
48149	Metformin 500mg tablets (Almus Pharmaceuticals Ltd)
49502	Glucophage SR 500mg tablets (Mawdsley-Brooks & Company Ltd)
49738	Metformin 1g modified-release tablets (A A H Pharmaceuticals Ltd)
50821	Metformin 850mg tablets (Pfizer Ltd)
50970	Metformin 500mg tablets (Bristol Laboratories Ltd)

51135	Metformin 500mg modified-release tablets (A A H Pharmaceuticals Ltd)
51527	Metformin 500mg tablets (Boston Healthcare Ltd)
52442	Metformin 500mg tablets (Pfizer Ltd)
52634	Glucophage SR 500mg tablets (Doncaster Pharmaceuticals Ltd)
53478	Metformin 500mg modified-release tablets (Kent Pharmaceuticals Ltd)
53867	Metformin 500mg tablets (Zentiva)
54442	Metformin (roi) 1000mg Tablet
54898	Metformin 850mg tablets (Almus Pharmaceuticals Ltd)
55270	Duformin 500mg Tablet (Dumex Ltd)
55739	Metformin 500mg tablets (Tillomed Laboratories Ltd)
57457	Metformin 500mg tablets (Aurobindo Pharma Ltd)
58607	Metformin 500mg/5ml oral solution sugar free (Zentiva)
59620	Glucophage SR 500mg tablets (Waymade Healthcare Plc)
60074	Metformin 1g modified-release tablets (Waymade Healthcare Plc)
60968	Metformin 500mg modified-release tablets (Actavis UK Ltd)
62144	Metformin 500mg modified-release tablets (DE Pharmaceuticals)
62265	Metformin 500mg modified-release tablets (Mawdsley-Brooks & Company Ltd)
18220	Pioglitazone 15mg / Metformin 850mg tablets
7375	Rosiglitazone 4mg / Metformin 1g tablets
11717	Rosiglitazone 2mg / Metformin 1g tablets
7325	Avandamet 4mg/1000mg tablets (GlaxoSmithKline UK Ltd)
14164	Avandamet 2mg/1000mg tablets (GlaxoSmithKline UK Ltd)
11601	Rosiglitazone 2mg / Metformin 500mg tablets
6855	Avandamet 2mg/500mg tablets (GlaxoSmithKline UK Ltd)
37902	Vildagliptin 50mg / Metformin 1g tablets
31077	Competact 15mg/850mg tablets (Takeda UK Ltd)
43619	Metformin 1g / Sitagliptin 50mg tablets
30316	Metformin with pioglitazone 850mg + 15mg Tablet
37874	Vildagliptin 50mg / Metformin 850mg tablets
11760	Metformin with rosiglitazone 1000mg + 2mg Tablet
43684	Janumet 50mg/1000mg tablets (Merck Sharp & Dohme Ltd)
11737	Metformin with rosiglitazone 1000mg + 4mg Tablet
11610	Metformin with rosiglitazone 500mg + 2mg Tablet
17580	Avandamet 1mg/500mg tablets (GlaxoSmithKline UK Ltd)
11604	Rosiglitazone 1mg / Metformin 500mg tablets
38551	Eucreas 50mg/1000mg tablets (Novartis Pharmaceuticals UK Ltd)
39203	Eucreas 50mg/850mg tablets (Novartis Pharmaceuticals UK Ltd)
11609	Metformin with rosiglitazone 500mg + 1mg Tablet
59385	Vipdomet 12.5mg/1000mg tablets (Takeda UK Ltd)
52445	Linagliptin 2.5mg / Metformin 1g tablets
50682	Jentadueto 2.5mg/1000mg tablets (Boehringer Ingelheim Ltd)
54891	Saxagliptin 2.5mg / Metformin 1g tablets
52449	Linagliptin 2.5mg / Metformin 850mg tablets
54150	Jentadueto 2.5mg/850mg tablets (Boehringer Ingelheim Ltd)
60012	Dapagliflozin 5mg / Metformin 1g tablets
54973	Saxagliptin 2.5mg / Metformin 850mg tablets
56965	Komboglyze 2.5mg/1000mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)

58865	Komboglyze 2.5mg/850mg tablets (AstraZeneca UK Ltd)
60643	Xigduo 5mg/1000mg tablets (AstraZeneca UK Ltd)
60497	Alogliptin 12.5mg / Metformin 1g tablets
32	Gliclazide 80mg tablets
1254	Glibenclamide 5mg tablets
5627	Gliclazide 30mg modified-release tablets
5636	Glipizide 5mg tablets
1965	Tolbutamide 500mg tablets
2219	Glibenclamide 2.5mg tablets
5316	Glimepiride 4mg tablets
5353	Glimepiride 2mg tablets
1964	Diamicron 80mg tablets (Servier Laboratories Ltd)
5276	Glimepiride 1mg tablets
6337	Glimepiride 3mg tablets
43065	Gliclazide 40mg tablets
547	Glipizide 2.5mg tablets
7744	Daonil 5mg tablets (Sanofi)
11695	Diamicron 30mg MR tablets (Servier Laboratories Ltd)
1847	Chlorpropamide 250mg tablets
12513	Glibenese 5mg tablets (Pfizer Ltd)
13331	Euglucon 5mg tablets (Sanofi)
1253	Chlorpropamide 100mg tablets
7912	Semi-Daonil 2.5mg tablets (Sanofi)
8168	Diabinese 250mg Tablet (Pfizer Ltd)
21832	Diabetamide 5mg tablets (Ashbourne Pharmaceuticals Ltd)
8034	Diabinese 100mg Tablet (Pfizer Ltd)
17698	Minodiab 5mg tablets (Pfizer Ltd)
7332	Amaryl 1mg tablets (Zentiva)
7284	Amaryl 2mg tablets (Zentiva)
11284	Amaryl 4mg tablets (Zentiva)
7409	Amaryl 3mg tablets (Zentiva)
12455	Rastinon 500mg Tablet (Hoechst Marion Roussel)
8976	Euglucon 2.5mg tablets (Aventis Pharma)
4862	Diabetamide 2.5mg tablets (Ashbourne Pharmaceuticals Ltd)
17706	Minodiab 2.5mg tablets (Pfizer Ltd)
8390	Gliquidone 30mg tablets
26218	Calabren 5mg Tablet (Berk Pharmaceuticals Ltd)
17343	Gliclazide 80mg tablets (A A H Pharmaceuticals Ltd)
15374	Gliclazide 40mg/5ml oral suspension
21892	Diaglyk 80mg tablets (Ashbourne Pharmaceuticals Ltd)
31212	Gliclazide 80mg tablets (Actavis UK Ltd)
10427	Tolazamide 250mg Tablet
19658	Glurenorm 30mg tablets (Sanofi)
22145	Tolanase 100mg Tablet (Pharmacia Ltd)
34399	Gliclazide 80mg tablets (IVAX Pharmaceuticals UK Ltd)
21489	Tolanase 250mg Tablet (Pharmacia Ltd)
16602	Calabren 2.5mg Tablet (Berk Pharmaceuticals Ltd)

4426	CHLORPROPAMIDE 500 MG TAB
41558	Glibenclamide 5mg tablets (Teva UK Ltd)
56437	Gliclazide 60mg modified-release tablets
42790	Gliclazide 80mg Tablet (Merck Generics (UK) Ltd)
21424	Glibenclamide 5mg/5ml oral suspension
40425	Nazdol MR 30mg tablets (Teva UK Ltd)
41593	Glibenclamide 2.5mg tablets (Teva UK Ltd)
33673	Tolbutamide 500mg tablets (Actavis UK Ltd)
29939	Gliclazide 80mg tablets (Generics (UK) Ltd)
47074	Gliclazide 80mg/5ml oral suspension
29326	Glipizide 5mg tablets (Generics (UK) Ltd)
31474	Libanil 5mg Tablet (Approved Prescription Services Ltd)
41559	Glibenclamide 5mg tablets (A A H Pharmaceuticals Ltd)
34957	Tolbutamide 500mg tablets (A A H Pharmaceuticals Ltd)
9108	TOLBUTAMIDE 250 MG TAB
43465	Zicron 40mg tablets (Bristol Laboratories Ltd)
46927	Tolbutamide 500mg tablets (Teva UK Ltd)
55862	Gliclazide Oral solution
34563	Glibenclamide 5mg tablets (Wockhardt UK Ltd)
34507	Glibenclamide 2.5mg tablets (Wockhardt UK Ltd)
36856	Gliclazide 80mg tablets (Sandoz Ltd)
41898	GLIBENCLAMIDE
21564	Gliclazide 80mg tablets (Wockhardt UK Ltd)
16211	TOLBUTAMIDE 100 MG TAB
34802	Glipizide 5mg tablets (IVAX Pharmaceuticals UK Ltd)
44473	Edicil MR 30mg tablets (Ratiopharm UK Ltd)
22636	TOLBUTAMIDE 1 GM TAB
22858	Acetohexamide 500mg tablets
26118	Dimelor 500mg Tablet (Eli Lilly and Company Ltd)
45215	Gliclazide 80mg Tablet (Neo Laboratories Ltd)
12245	Glutril 25mg Tablet (Roche Products Ltd)
12259	Glibornuride 25mg Tablet
34676	Glibenclamide 2.5mg tablets (A A H Pharmaceuticals Ltd)
34706	Glibenclamide 2.5mg tablets (IVAX Pharmaceuticals UK Ltd)
24848	Glymidine sodium 500mg Tablet
47894	Nazdol MR 30mg tablets (Consilient Health Ltd)
60495	Gliclazide 80mg tablets (Teva UK Ltd)
34932	Gliclazide 80mg tablets (Genus Pharmaceuticals Ltd)
25636	Libanil 2.5mg Tablet (Approved Prescription Services Ltd)
40365	Glimepiride 1mg tablets (Actavis UK Ltd)
58882	Gliclazide 120mg/5ml oral suspension
27969	Glymese 250mg Tablet (DDSA Pharmaceuticals Ltd)
28708	Malix 2.5mg Tablet (Lagap)
30460	Malix 5mg Tablet (Lagap)
33562	Duclazide 80mg Tablet (Dumex Ltd)
44304	Glyconon 500mg Tablet (DDSA Pharmaceuticals Ltd)
44738	Niddaryl 1mg tablets (Dee Pharmaceuticals Ltd)

51955	Gliclazide 80mg tablets (Accord Healthcare Ltd)
53288	Gliclazide 30mg modified-release tablets (A A H Pharmaceuticals Ltd)
57601	Daonil 5mg tablets (Dowelhurst Ltd)
62034	Laaglyda MR 60mg tablets (Consilient Health Ltd)
11946	Tolbutamide 50mg/ml Injection
48056	Gliclazide 80mg tablets (Sovereign Medical Ltd)
54764	Gliclazide 80mg tablets (Arrow Generics Ltd)
56008	Gliclazide 80mg tablets (Almus Pharmaceuticals Ltd)
56376	Rosiglitazone 4mg with glimepiride 4mg tablet
57830	Gliclazide 30mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)
61311	Glimepiride 4mg tablets (Sigma Pharmaceuticals Plc)
61957	Gliclazide 40mg tablets (A A H Pharmaceuticals Ltd)
62014	Glimepiride 2mg tablets (Accord Healthcare Ltd)
35022	Sitagliptin 100mg tablets
469	Rosiglitazone 4mg tablets
9699	Pioglitazone 30mg tablets
548	Pioglitazone 15mg tablets
10051	Pioglitazone 45mg tablets
5227	Rosiglitazone 8mg tablets
479	Acarbose 50mg tablets
40693	Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices
35149	Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices
5174	Acarbose 100mg tablets
41204	Saxagliptin 5mg tablets
9748	Repaglinide 2mg tablets
5621	Glucobay 50mg tablets (Bayer Plc)
9707	Repaglinide 1mg tablets
40642	Victoza 6mg/ml solution for injection 3ml pre-filled pen (Novo Nordisk Ltd)
35150	Byetta 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices (Bristol-Myers Squibb Pharmaceuticals Ltd)
37875	Vildagliptin 50mg tablets
9865	Repaglinide 500microgram tablets
46665	Linagliptin 5mg tablets
35462	Januvia 100mg tablets (Merck Sharp & Dohme Ltd)
9662	Avandia 4mg tablets (GlaxoSmithKline UK Ltd)
45775	Saxagliptin 2.5mg tablets
11483	Nateglinide 60mg tablets
9105	Glucobay 100mg tablets (Bayer Plc)
35251	Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices
20889	Actos 30mg tablets (Takeda UK Ltd)
5678	Nateglinide 120mg tablets
48401	Sitagliptin 50mg tablets
46469	Bydureon 2mg powder and solvent for suspension for injection vials (Bristol-Myers Squibb Pharmaceuticals Ltd)
11366	NovoNorm 2mg tablets (Novo Nordisk Ltd)
15232	Avandia 8mg tablets (GlaxoSmithKline UK Ltd)
11321	NovoNorm 1mg tablets (Novo Nordisk Ltd)
5989	Nateglinide 180mg tablets

35144	Byetta 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices (Bristol-Myers Squibb Pharmaceuticals Ltd)
20287	Actos 15mg tablets (Takeda UK Ltd)
11316	NovoNorm 500microgram tablets (Novo Nordisk Ltd)
48533	Sitagliptin 25mg tablets
7695	Guarem Sachets (Shire Pharmaceuticals Ltd)
19472	Actos 45mg tablets (Takeda UK Ltd)
46458	Exenatide 2mg powder and solvent for suspension for injection vials
46716	Trajenta 5mg tablets (Boehringer Ingelheim Ltd)
23945	Starlix 60mg tablets (Novartis Pharmaceuticals UK Ltd)
19336	Tolazamide 100mg Tablet
54182	Dapagliflozin 10mg tablets
15955	Starlix 120mg tablets (Novartis Pharmaceuticals UK Ltd)
41431	Onglyza 5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
3740	Guar gum 90% granules
27125	Starlix 180mg tablets (Novartis Pharmaceuticals UK Ltd)
54203	Forxiga 10mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
60211	Canagliflozin 100mg tablets
35561	Prandin 2mg tablets (Novo Nordisk Ltd)
36774	Prandin 1mg tablets (Novo Nordisk Ltd)
54265	Dapagliflozin 5mg tablets
59177	Alogliptin 25mg tablets
55413	Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
12897	Guar gum 5g granules sachets sugar free
4307	Guarina Sachets (Norgine Pharmaceuticals Ltd)
36948	Prandin 0.5mg tablets (Novo Nordisk Ltd)
39149	Galvus 50mg tablets (Novartis Pharmaceuticals UK Ltd)
50087	Januvia 50mg tablets (Merck Sharp & Dohme Ltd)
54480	Forxiga 5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
55729	Lyxumia 20micrograms/0.2ml solution for injection 3ml pre-filled pen (Sanofi)
45821	Onglyza 2.5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)
50124	Januvia 25mg tablets (Merck Sharp & Dohme Ltd)
55459	Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
60430	Invokana 100mg tablets (Janssen-Cilag Ltd)
55723	Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices and Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices
60386	Canagliflozin 300mg tablets
60328	Alogliptin 12.5mg tablets
55728	Lyxumia 10micrograms/0.2ml solution for injection 3ml pre-filled pen (Sanofi)
45831	Dacadis MR 30mg tablets (Generics (UK) Ltd)
55767	Lyxumia 10micrograms/0.2ml solution for injection 3ml pre-filled pen and Lyxumia 20micrograms/0.2ml solution for injection 3ml pre-filled pen (Sanofi)
59809	Alogliptin 6.25mg tablets
7745	GUAR GUM TAB
61756	Empagliflozin 10mg tablets
60379	Invokana 300mg tablets (Janssen-Cilag Ltd)
37617	Rosiglitazone 2mg tablet
60073	Canagliflozin 100mg tablets
56208	Pioglitazone 15mg tablets (A A H Pharmaceuticals Ltd)

60682	Vipidia 25mg tablets (Takeda UK Ltd)
60681	Vipidia 12.5mg tablets (Takeda UK Ltd)
60066	Invokana 100mg tablets (Janssen-Cilag Ltd)
13628	Romozin 400mg Tablet (Glaxo Wellcome UK Ltd)
52203	Enyglid 0.5mg tablets (Consilient Health Ltd)
56831	Troglitazone 200mg Tablet
62172	Empagliflozin 25mg tablets
48120	Avandia 2mg Tablet (GlaxoSmithKline UK Ltd)
48139	Pioglitazone 30mg tablets (A A H Pharmaceuticals Ltd)
57659	Pioglitazone 30mg tablets (Actavis UK Ltd)
61925	NovoNorm 500microgram tablets (Waymade Healthcare Plc)

Codes for exclusion

medcode	readcode	readterm
33969	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
52236	C10A.00	Malnutrition-related diabetes mellitus
66675	C10A000	Malnutrition-related diabetes mellitus with coma
100347	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
109133	L180700	Pre-existing malnutrition-related diabetes mellitus
46624	C10C.11	Maturity onset diabetes in youth
21472	Q441.00	Neonatal diabetes mellitus
59991	C10D.11	Maturity onset diabetes in youth type 2
98392	C10C.12	Maturity onset diabetes in youth type 1
2983	C350000	Haemochromatosis
23479	C350011	Bronzed diabetes
106557	Q47y100	Bronze baby
11551	C10B.00	Diabetes mellitus induced by steroids
32193	C11y000	Steroid induced diabetes
26108	C10B000	Steroid induced diabetes mellitus without complication
61122	C10H.00	Diabetes mellitus induced by non-steroid drugs
8446	L180811	Gestational diabetes mellitus
2664	L180900	Gestational diabetes mellitus
11359	L180.00	Diabetes mellitus during pregnancy/childbirth/puerperium
94777	ZV13F00	[V]Personal history of gestational diabetes mellitus
10278	L180800	Diabetes mellitus arising in pregnancy
104588	66Ay.00	Gestational diabetes mellitus annual review
46577	66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet
34639	L180100	Diabetes mellitus during pregnancy - baby delivered
64384	L180z00	Diabetes mellitus in pregnancy/childbirth/puerperium NOS
49559	L180300	Diabetes mellitus during pregnancy - baby not yet delivered
67635	L180000	Diabetes mellitus - unspec whether in pregnancy/puerperium
96823	L180400	Diabetes mellitus in pueperium - baby previously delivered
108013	ZC2CB00	Dietary advice for gestational diabetes

Cancer codes

medcode	readcode	readterm
19415	B0...00	Malignant neoplasm of lip, oral cavity and pharynx
24374	B0...11	Carcinoma of lip, oral cavity and pharynx
14712	B00..00	Malignant neoplasm of lip
9984	B00..11	Carcinoma of lip
73962	B000.00	Malignant neoplasm of upper lip, vermilion border
66270	B000000	Malignant neoplasm of upper lip, external
50296	B000100	Malignant neoplasm of upper lip, lipstick area
98740	B000z00	Malignant neoplasm of upper lip, vermilion border NOS
67446	B001.00	Malignant neoplasm of lower lip, vermilion border
66384	B001000	Malignant neoplasm of lower lip, external
95480	B001100	Malignant neoplasm of lower lip, lipstick area
101707	B001z00	Malignant neoplasm of lower lip, vermilion border NOS
99493	B002.00	Malignant neoplasm of upper lip, inner aspect
99001	B002100	Malignant neoplasm of upper lip, frenulum
98500	B002200	Malignant neoplasm of upper lip, mucosa
90610	B002300	Malignant neoplasm of upper lip, oral aspect
100721	B002z00	Malignant neoplasm of upper lip, inner aspect NOS
71147	B003.00	Malignant neoplasm of lower lip, inner aspect
67504	B003000	Malignant neoplasm of lower lip, buccal aspect
91843	B003100	Malignant neoplasm of lower lip, frenulum
89909	B003200	Malignant neoplasm of lower lip, mucosa
94441	B003300	Malignant neoplasm of lower lip, oral aspect
96782	B003z00	Malignant neoplasm of lower lip, inner aspect NOS
61692	B004.00	Malignant neoplasm of lip unspecified, inner aspect
73614	B004000	Malignant neoplasm of lip unspecified, buccal aspect
68399	B004200	Malignant neoplasm of lip unspecified, mucosa
100144	B004300	Malignant neoplasm of lip, oral aspect
96783	B005.00	Malignant neoplasm of commissure of lip
18882	B006.00	Malignant neoplasm of overlapping lesion of lip
37553	B007.00	Malignant neoplasm of lip, unspecified
100906	B00z000	Malignant neoplasm of lip, unspecified, external
94251	B00z100	Malignant neoplasm of lip, unspecified, lipstick area
69761	B00zz00	Malignant neoplasm of lip, vermilion border NOS
10283	B01..00	Malignant neoplasm of tongue
43431	B010.00	Malignant neoplasm of base of tongue
69671	B010.11	Malignant neoplasm of posterior third of tongue
34409	B010000	Malignant neoplasm of base of tongue dorsal surface
91035	B010z00	Malignant neoplasm of fixed part of tongue NOS
43642	B011.00	Malignant neoplasm of dorsal surface of tongue
43781	B011z00	Malignant neoplasm of dorsum of tongue NOS
36161	B012.00	Malignant neoplasm of tongue, tip and lateral border
62840	B013.00	Malignant neoplasm of ventral surface of tongue

102142	B013000	Malignant neoplasm of anterior 2/3 of tongue ventral surface
63979	B013100	Malignant neoplasm of frenulum linguae
38488	B013z00	Malignant neoplasm of ventral tongue surface NOS
58121	B014.00	Malignant neoplasm of anterior 2/3 of tongue unspecified
37096	B015.00	Malignant neoplasm of tongue, junctional zone
24852	B016.00	Malignant neoplasm of lingual tonsil
47205	B017.00	Malignant overlapping lesion of tongue
41530	B01y.00	Malignant neoplasm of other sites of tongue
40557	B01z.00	Malignant neoplasm of tongue NOS
20292	B02..00	Malignant neoplasm of major salivary glands
4388	B020.00	Malignant neoplasm of parotid gland
51786	B021.00	Malignant neoplasm of submandibular gland
70928	B022.00	Malignant neoplasm of sublingual gland
70696	B02y.00	Malignant neoplasm of other major salivary glands
50475	B02z.00	Malignant neoplasm of major salivary gland NOS
43400	B03..00	Malignant neoplasm of gum
32024	B030.00	Malignant neoplasm of upper gum
49360	B031.00	Malignant neoplasm of lower gum
101753	B03y.00	Malignant neoplasm of other sites of gum
93218	B03z.00	Malignant neoplasm of gum NOS
20092	B04..00	Malignant neoplasm of floor of mouth
45408	B040.00	Malignant neoplasm of anterior portion of floor of mouth
45986	B041.00	Malignant neoplasm of lateral portion of floor of mouth
17912	B042.00	Malignant neoplasm, overlapping lesion of floor of mouth
56709	B04y.00	Malignant neoplasm of other sites of floor of mouth
36716	B04z.00	Malignant neoplasm of floor of mouth NOS
14792	B05..00	Malignant neoplasm of other and unspecified parts of mouth
31364	B050.00	Malignant neoplasm of cheek mucosa
30402	B050.11	Malignant neoplasm of buccal mucosa
103796	B051.00	Malignant neoplasm of vestibule of mouth
95772	B051000	Malignant neoplasm of upper buccal sulcus
97530	B051100	Malignant neoplasm of lower buccal sulcus
37590	B052.00	Malignant neoplasm of hard palate
40292	B053.00	Malignant neoplasm of soft palate
37516	B054.00	Malignant neoplasm of uvula
70819	B055.00	Malignant neoplasm of palate unspecified
96003	B055000	Malignant neoplasm of junction of hard and soft palate
69951	B055100	Malignant neoplasm of roof of mouth
28559	B055z00	Malignant neoplasm of palate NOS
37724	B056.00	Malignant neoplasm of retromolar area
10314	B057.00	Overlapping lesion of other and unspecified parts of mouth
37916	B05y.00	Malignant neoplasm of other specified mouth parts
55015	B05z.00	Malignant neoplasm of mouth NOS
37549	B05z000	Kaposi's sarcoma of palate
22893	B06..00	Malignant neoplasm of oropharynx

16241	B060.00	Malignant neoplasm of tonsil
26448	B060000	Malignant neoplasm of faucial tonsil
101988	B060100	Malignant neoplasm of palatine tonsil
102151	B060200	Malignant neoplasm of overlapping lesion of tonsil
53884	B060z00	Malignant neoplasm tonsil NOS
24397	B061.00	Malignant neoplasm of tonsillar fossa
55066	B062.00	Malignant neoplasm of tonsillar pillar
51926	B062000	Malignant neoplasm of faucial pillar
99185	B062100	Malignant neoplasm of glossopalatine fold
61510	B062200	Malignant neoplasm of palatoglossal arch
93842	B062300	Malignant neoplasm of palatopharyngeal arch
100002	B062z00	Malignant neoplasm of tonsillar fossa NOS
39554	B063.00	Malignant neoplasm of vallecula
46728	B064.00	Malignant neoplasm of anterior epiglottis
26134	B064000	Malignant neoplasm of epiglottis, free border
91895	B064100	Malignant neoplasm of glossoepiglottic fold
73439	B064z00	Malignant neoplasm of anterior epiglottis NOS
48519	B065.00	Malignant neoplasm of junctional region of epiglottis
56355	B066.00	Malignant neoplasm of lateral wall of oropharynx
90124	B067.00	Malignant neoplasm of posterior wall of oropharynx
67323	B06y.00	Malignant neoplasm of oropharynx, other specified sites
91037	B06yz00	Malignant neoplasm of other specified site of oropharynx NOS
43200	B06z.00	Malignant neoplasm of oropharynx NOS
24675	B07..00	Malignant neoplasm of nasopharynx
94390	B070.00	Malignant neoplasm of roof of nasopharynx
95429	B071.00	Malignant neoplasm of posterior wall of nasopharynx
33388	B071000	Malignant neoplasm of adenoid
46548	B071100	Malignant neoplasm of pharyngeal tonsil
96869	B071z00	Malignant neoplasm of posterior wall of nasopharynx NOS
59004	B072.00	Malignant neoplasm of lateral wall of nasopharynx
37940	B072000	Malignant neoplasm of pharyngeal recess
102205	B072z00	Malignant neoplasm of lateral wall of nasopharynx NOS
44139	B073.00	Malignant neoplasm of anterior wall of nasopharynx
99386	B073200	Malignant neoplasm posterior margin nasal septum and choanae
100918	B073z00	Malignant neoplasm of anterior wall of nasopharynx NOS
66422	B074.00	Malignant neoplasm, overlapping lesion of nasopharynx
55630	B07y.00	Malignant neoplasm of other specified site of nasopharynx
28665	B07z.00	Malignant neoplasm of nasopharynx NOS
34012	B08..00	Malignant neoplasm of hypopharynx
43548	B080.00	Malignant neoplasm of postcricoid region
39897	B081.00	Malignant neoplasm of pyriform sinus
57248	B082.00	Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect
64462	B083.00	Malignant neoplasm of posterior pharynx
88362	B08y.00	Malignant neoplasm of other specified hypopharyngeal site
28451	B08z.00	Malignant neoplasm of hypopharynx NOS

46114	B0z..00	Malig neop other/ill-defined sites lip, oral cavity, pharynx
16297	B0z0.00	Malignant neoplasm of pharynx unspecified
95016	B0z1.00	Malignant neoplasm of Waldeyer's ring
39084	B0z2.00	Malignant neoplasm of laryngopharynx
49758	B0zy.00	Malignant neoplasm of other sites lip, oral cavity, pharynx
39430	B0zz.00	Malignant neoplasm of lip, oral cavity and pharynx NOS
15709	B1...00	Malignant neoplasm of digestive organs and peritoneum
3357	B1...11	Carcinoma of digestive organs and peritoneum
1062	B10..00	Malignant neoplasm of oesophagus
61695	B100.00	Malignant neoplasm of cervical oesophagus
41362	B101.00	Malignant neoplasm of thoracic oesophagus
63470	B102.00	Malignant neoplasm of abdominal oesophagus
50789	B103.00	Malignant neoplasm of upper third of oesophagus
54171	B104.00	Malignant neoplasm of middle third of oesophagus
42416	B105.00	Malignant neoplasm of lower third of oesophagus
67497	B106.00	Malignant neoplasm, overlapping lesion of oesophagus
98142	B107.00	Siewert type I adenocarcinoma
53591	B10y.00	Malignant neoplasm of other specified part of oesophagus
30700	B10z.00	Malignant neoplasm of oesophagus NOS
4865	B10z.11	Oesophageal cancer
8386	B11..00	Malignant neoplasm of stomach
10368	B11..11	Gastric neoplasm
32022	B110.00	Malignant neoplasm of cardia of stomach
100584	B110000	Malignant neoplasm of cardiac orifice of stomach
22894	B110100	Malignant neoplasm of cardio-oesophageal junction of stomach
94278	B110111	Malignant neoplasm of gastro-oesophageal junction
37859	B110z00	Malignant neoplasm of cardia of stomach NOS
21620	B111.00	Malignant neoplasm of pylorus of stomach
48237	B111000	Malignant neoplasm of prepylorus of stomach
41215	B111100	Malignant neoplasm of pyloric canal of stomach
59092	B111z00	Malignant neoplasm of pylorus of stomach NOS
19318	B112.00	Malignant neoplasm of pyloric antrum of stomach
32362	B113.00	Malignant neoplasm of fundus of stomach
43572	B114.00	Malignant neoplasm of body of stomach
42193	B115.00	Malignant neoplasm of lesser curve of stomach unspecified
55434	B116.00	Malignant neoplasm of greater curve of stomach unspecified
51690	B117.00	Malignant neoplasm, overlapping lesion of stomach
97499	B118.00	Siewert type II adenocarcinoma
96094	B119.00	Siewert type III adenocarcinoma
55019	B11y.00	Malignant neoplasm of other specified site of stomach
65312	B11y000	Malignant neoplasm of anterior wall of stomach NEC
96802	B11y100	Malignant neoplasm of posterior wall of stomach NEC
65372	B11yz00	Malignant neoplasm of other specified site of stomach NOS
14800	B11z.00	Malignant neoplasm of stomach NOS
6806	B12..00	Malignant neoplasm of small intestine and duodenum

18613	B120.00	Malignant neoplasm of duodenum
43479	B121.00	Malignant neoplasm of jejunum
33871	B122.00	Malignant neoplasm of ileum
63995	B123.00	Malignant neoplasm of Meckel's diverticulum
66166	B124.00	Malignant neoplasm, overlapping lesion of small intestine
99896	B12y.00	Malignant neoplasm of other specified site small intestine
43390	B12z.00	Malignant neoplasm of small intestine NOS
1220	B13..00	Malignant neoplasm of colon
9088	B130.00	Malignant neoplasm of hepatic flexure of colon
6935	B131.00	Malignant neoplasm of transverse colon
10864	B132.00	Malignant neoplasm of descending colon
2815	B133.00	Malignant neoplasm of sigmoid colon
3811	B134.00	Malignant neoplasm of caecum
22163	B134.11	Carcinoma of caecum
18632	B135.00	Malignant neoplasm of appendix
10946	B136.00	Malignant neoplasm of ascending colon
18619	B137.00	Malignant neoplasm of splenic flexure of colon
93478	B138.00	Malignant neoplasm, overlapping lesion of colon
101700	B139.00	Hereditary nonpolyposis colon cancer
48231	B13y.00	Malignant neoplasm of other specified sites of colon
28163	B13z.00	Malignant neoplasm of colon NOS
9118	B13z.11	Colonic cancer
35357	B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
27855	B140.00	Malignant neoplasm of rectosigmoid junction
1800	B141.00	Malignant neoplasm of rectum
7219	B141.11	Carcinoma of rectum
5901	B141.12	Rectal carcinoma
24370	B142.00	Malignant neoplasm of anal canal
9491	B142.11	Anal carcinoma
46159	B142000	Malignant neoplasm of cloacogenic zone
27897	B143.00	Malignant neoplasm of anus unspecified
55659	B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
50974	B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
8918	B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
25535	B150.00	Primary malignant neoplasm of liver
16126	B150000	Primary carcinoma of liver
31210	B150100	Hepatoblastoma of liver
68410	B150200	Primary angiosarcoma of liver
22187	B150300	Hepatocellular carcinoma
44399	B150z00	Primary malignant neoplasm of liver NOS
16915	B151.00	Malignant neoplasm of intrahepatic bile ducts
65124	B151000	Malignant neoplasm of interlobular bile ducts
89593	B151200	Malignant neoplasm of intrahepatic biliary passages
58088	B151400	Malignant neoplasm of intrahepatic gall duct
61643	B151z00	Malignant neoplasm of intrahepatic bile ducts NOS

26393	B152.00	Malignant neoplasm of liver unspecified
36147	B153.00	Secondary malignant neoplasm of liver
38978	B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
54103	B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
16105	B160.00	Malignant neoplasm of gallbladder
31393	B160.11	Carcinoma gallbladder
23433	B161.00	Malignant neoplasm of extrahepatic bile ducts
72445	B161000	Malignant neoplasm of cystic duct
52537	B161100	Malignant neoplasm of hepatic duct
7982	B161200	Malignant neoplasm of common bile duct
36495	B161211	Carcinoma common bile duct
74896	B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
10949	B162.00	Malignant neoplasm of ampulla of Vater
35039	B163.00	Malignant neoplasm, overlapping lesion of biliary tract
60312	B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
15907	B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
8166	B17..00	Malignant neoplasm of pancreas
8771	B170.00	Malignant neoplasm of head of pancreas
40810	B171.00	Malignant neoplasm of body of pancreas
39870	B172.00	Malignant neoplasm of tail of pancreas
35535	B173.00	Malignant neoplasm of pancreatic duct
35795	B174.00	Malignant neoplasm of Islets of Langerhans
97875	B175.00	Malignant neoplasm, overlapping lesion of pancreas
48537	B17y.00	Malignant neoplasm of other specified sites of pancreas
96635	B17y000	Malignant neoplasm of ectopic pancreatic tissue
95783	B17yz00	Malignant neoplasm of specified site of pancreas NOS
34388	B17z.00	Malignant neoplasm of pancreas NOS
44108	B18..00	Malignant neoplasm of retroperitoneum and peritoneum
21330	B180.00	Malignant neoplasm of retroperitoneum
65159	B180100	Malignant neoplasm of perinephric tissue
24048	B180200	Malignant neoplasm of retrocaecal tissue
61555	B180z00	Malignant neoplasm of retroperitoneum NOS
17874	B181.00	Mesothelioma of peritoneum
101907	B182.00	Overlapping malign lesion of retroperitoneum and peritoneum
46613	B18y.00	Malignant neoplasm of specified parts of peritoneum
59388	B18y100	Malignant neoplasm of mesocaecum
30165	B18y200	Malignant neoplasm of mesorectum
50898	B18y300	Malignant neoplasm of omentum
64516	B18y400	Malignant neoplasm of parietal peritoneum
39413	B18y500	Malignant neoplasm of pelvic peritoneum
69821	B18y600	Malignant neoplasm of the pouch of Douglas
90290	B18y700	Malignant neoplasm of mesentery
64106	B18yz00	Malignant neoplasm of specified parts of peritoneum NOS
16298	B18z.00	Malignant neoplasm of retroperitoneum and peritoneum NOS
11009	B1z..00	Malig neop oth/ill-defined sites digestive tract/peritoneum

17559	B1z0.00	Malignant neoplasm of intestinal tract, part unspecified
11628	B1z0.11	Cancer of bowel
65460	B1z1.00	Malignant neoplasm of spleen NEC
72224	B1z1100	Fibrosarcoma of spleen
93778	B1z1z00	Malignant neoplasm of spleen NOS
94776	B1z2.00	Malignant neoplasm, overlapping lesion of digestive system
56918	B1zy.00	Malignant neoplasm other spec digestive tract and peritoneum
51255	B1zz.00	Malignant neoplasm of digestive tract and peritoneum NOS
34075	B2...00	Malig neop of respiratory tract and intrathoracic organs
45307	B2...11	Carcinoma of respiratory tract and intrathoracic organs
26652	B20..00	Malig neop nasal cavities, middle ear and accessory sinuses
23389	B200.00	Malignant neoplasm of nasal cavities
71204	B200000	Malignant neoplasm of cartilage of nose
98911	B200100	Malignant neoplasm of nasal conchae
62761	B200200	Malignant neoplasm of septum of nose
62182	B200300	Malignant neoplasm of vestibule of nose
42856	B200z00	Malignant neoplasm of nasal cavities NOS
24456	B201.00	Malig neop auditory tube, middle ear and mastoid air cells
98537	B201100	Malignant neoplasm of tympanic cavity
54613	B201200	Malignant neoplasm of tympanic antrum
71946	B201300	Malignant neoplasm of mastoid air cells
73537	B201z00	Malig neop auditory tube, middle ear, mastoid air cells NOS
32174	B202.00	Malignant neoplasm of maxillary sinus
54636	B203.00	Malignant neoplasm of ethmoid sinus
15684	B204.00	Malignant neoplasm of frontal sinus
65215	B205.00	Malignant neoplasm of sphenoidal sinus
39590	B206.00	Malignant neoplasm, overlapping lesion of accessory sinuses
96971	B20y.00	Malig neop other site nasal cavity, middle ear and sinuses
55246	B20z.00	Malignant neoplasm of accessory sinus NOS
319	B21..00	Malignant neoplasm of larynx
318	B210.00	Malignant neoplasm of glottis
26165	B211.00	Malignant neoplasm of supraglottis
22441	B212.00	Malignant neoplasm of subglottis
43111	B213.00	Malignant neoplasm of laryngeal cartilage
63460	B213000	Malignant neoplasm of arytenoid cartilage
37805	B213100	Malignant neoplasm of cricoid cartilage
47862	B213300	Malignant neoplasm of thyroid cartilage
97332	B213z00	Malignant neoplasm of laryngeal cartilage NOS
50579	B214.00	Malignant neoplasm, overlapping lesion of larynx
55374	B215.00	Malignant neoplasm of epiglottis NOS
26813	B21y.00	Malignant neoplasm of larynx, other specified site
9237	B21z.00	Malignant neoplasm of larynx NOS
13243	B22..00	Malignant neoplasm of trachea, bronchus and lung
15221	B220.00	Malignant neoplasm of trachea
103946	B220100	Malignant neoplasm of mucosa of trachea

37810	B220z00	Malignant neoplasm of trachea NOS
12870	B221.00	Malignant neoplasm of main bronchus
17391	B221000	Malignant neoplasm of carina of bronchus
33444	B221100	Malignant neoplasm of hilus of lung
21698	B221z00	Malignant neoplasm of main bronchus NOS
10358	B222.00	Malignant neoplasm of upper lobe, bronchus or lung
20170	B222.11	Pancoast's syndrome
31700	B222000	Malignant neoplasm of upper lobe bronchus
25886	B222100	Malignant neoplasm of upper lobe of lung
44169	B222z00	Malignant neoplasm of upper lobe, bronchus or lung NOS
31268	B223.00	Malignant neoplasm of middle lobe, bronchus or lung
41523	B223000	Malignant neoplasm of middle lobe bronchus
39923	B223100	Malignant neoplasm of middle lobe of lung
54134	B223z00	Malignant neoplasm of middle lobe, bronchus or lung NOS
31188	B224.00	Malignant neoplasm of lower lobe, bronchus or lung
18678	B224000	Malignant neoplasm of lower lobe bronchus
12582	B224100	Malignant neoplasm of lower lobe of lung
42566	B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS
36371	B225.00	Malignant neoplasm of overlapping lesion of bronchus & lung
7484	B226.00	Mesothelioma
38961	B22y.00	Malignant neoplasm of other sites of bronchus or lung
3903	B22z.00	Malignant neoplasm of bronchus or lung NOS
2587	B22z.11	Lung cancer
31573	B23..00	Malignant neoplasm of pleura
67107	B230.00	Malignant neoplasm of parietal pleura
9600	B232.00	Mesothelioma of pleura
98104	B23y.00	Malignant neoplasm of other specified pleura
34742	B23z.00	Malignant neoplasm of pleura NOS
62556	B24..00	Malignant neoplasm of thymus, heart and mediastinum
27483	B240.00	Malignant neoplasm of thymus
95644	B241.00	Malignant neoplasm of heart
63430	B241000	Malignant neoplasm of endocardium
65605	B241200	Malignant neoplasm of myocardium
94975	B241300	Malignant neoplasm of pericardium
101885	B241400	Mesothelioma of pericardium
50289	B241z00	Malignant neoplasm of heart NOS
27715	B242.00	Malignant neoplasm of anterior mediastinum
92720	B243.00	Malignant neoplasm of posterior mediastinum
61064	B24X.00	Malignant neoplasm of mediastinum, part unspecified
100232	B24y.00	Malig neop of other site of heart, thymus and mediastinum
66750	B24z.00	Malignant neoplasm of heart, thymus and mediastinum NOS
39531	B25..00	Malig neo, overlapping lesion of heart, mediastinum & pleura
66646	B26..00	Malignant neoplasm, overlap lesion of resp & intrathor orgs
44356	B2z..00	Malig neop other/ill-defined sites resp/intrathoracic organs
65793	B2z0.00	Malig neop of upper respiratory tract, part unspecified

29283	B2zy.00	Malignant neoplasm of other site of respiratory tract
42569	B2zz.00	Malignant neoplasm of respiratory tract NOS
18608	B3...00	Malig neop of bone, connective tissue, skin and breast
9902	B3...11	Carcinoma of bone, connective tissue, skin and breast
12539	B3...12	Sarcoma of bone and connective tissue
18314	B30..00	Malignant neoplasm of bone and articular cartilage
5062	B30..11	Chondroma
29735	B30..12	Osteoma
59036	B300.00	Malignant neoplasm of bones of skull and face
53594	B300000	Malignant neoplasm of ethmoid bone
53599	B300100	Malignant neoplasm of frontal bone
59520	B300200	Malignant neoplasm of malar bone
95458	B300300	Malignant neoplasm of nasal bone
55953	B300400	Malignant neoplasm of occipital bone
50298	B300500	Malignant neoplasm of orbital bone
54747	B300600	Malignant neoplasm of parietal bone
55595	B300700	Malignant neoplasm of sphenoid bone
62104	B300800	Malignant neoplasm of temporal bone
50299	B300900	Malignant neoplasm of zygomatic bone
17475	B300A00	Malignant neoplasm of maxilla
96445	B300B00	Malignant neoplasm of turbinate
44452	B300C00	Malignant neoplasm of vomer
69146	B300z00	Malignant neoplasm of bones of skull and face NOS
33833	B301.00	Malignant neoplasm of mandible
16704	B302.00	Malignant neoplasm of vertebral column
46939	B302000	Malignant neoplasm of cervical vertebra
32372	B302100	Malignant neoplasm of thoracic vertebra
54691	B302200	Malignant neoplasm of lumbar vertebra
49701	B302z00	Malignant neoplasm of vertebral column NOS
27528	B303.00	Malignant neoplasm of ribs, sternum and clavicle
37842	B303000	Malignant neoplasm of rib
49491	B303100	Malignant neoplasm of sternum
66639	B303200	Malignant neoplasm of clavicle
60403	B303300	Malignant neoplasm of costal cartilage
67763	B303400	Malignant neoplasm of costo-vertebral joint
54493	B303500	Malignant neoplasm of xiphoid process
51237	B303z00	Malignant neoplasm of rib, sternum and clavicle NOS
71810	B304.00	Malignant neoplasm of scapula and long bones of upper arm
49054	B304000	Malignant neoplasm of scapula
61741	B304200	Malignant neoplasm of humerus
92371	B304300	Malignant neoplasm of radius
64848	B304400	Malignant neoplasm of ulna
65880	B304z00	Malig neop of scapula and long bones of upper arm NOS
73530	B305.00	Malignant neoplasm of hand bones
72464	B305.12	Malignant neoplasm of metacarpal bones

57988	B305000	Malignant neoplasm of carpal bone - scaphoid
69104	B305100	Malignant neoplasm of carpal bone - lunate
94427	B305C00	Malignant neoplasm of fifth metacarpal bone
86812	B305D00	Malignant neoplasm of phalanges of hand
73556	B305z00	Malignant neoplasm of hand bones NOS
54631	B306.00	Malignant neoplasm of pelvic bones, sacrum and coccyx
44609	B306000	Malignant neoplasm of ilium
59223	B306100	Malignant neoplasm of ischium
51921	B306200	Malignant neoplasm of pubis
40966	B306300	Malignant neoplasm of sacral vertebra
66908	B306400	Malignant neoplasm of coccygeal vertebra
50152	B306500	Malignant sacral teratoma
38938	B306z00	Malignant neoplasm of pelvis, sacrum or coccyx NOS
68055	B307.00	Malignant neoplasm of long bones of leg
56513	B307000	Malignant neoplasm of femur
50402	B307100	Malignant neoplasm of fibula
40814	B307200	Malignant neoplasm of tibia
62630	B307z00	Malignant neoplasm of long bones of leg NOS
95182	B308100	Malignant neoplasm of talus
72212	B308200	Malignant neoplasm of calcaneum
34878	B308300	Malignant neoplasm of medial cuneiform
69927	B308800	Malignant neoplasm of first metatarsal bone
92382	B308B00	Malignant neoplasm of fourth metatarsal bone
58949	B308D00	Malignant neoplasm of phalanges of foot
103354	B308z00	Malignant neoplasm of short bones of leg NOS
67451	B30W.00	Malignant neoplasm/overlap lesion/bone+articulr cartilage
43614	B30X.00	Malignant neoplasm/bones+articular cartilage/limb,unspfd
16075	B30z.00	Malignant neoplasm of bone and articular cartilage NOS
19437	B30z000	Osteosarcoma
34451	B31..00	Malignant neoplasm of connective and other soft tissue
43475	B310.00	Malig neop of connective and soft tissue head, face and neck
59382	B310000	Malignant neoplasm of soft tissue of head
40014	B310100	Malignant neoplasm of soft tissue of face
48517	B310200	Malignant neoplasm of soft tissue of neck
60035	B310300	Malignant neoplasm of cartilage of ear
49463	B310400	Malignant neoplasm of tarsus of eyelid
73718	B310z00	Malig neop connective and soft tissue head, face, neck NOS
53989	B311.00	Malig neop connective and soft tissue upper limb/shoulder
50222	B311000	Malignant neoplasm of connective and soft tissue of shoulder
64345	B311100	Malignant neoplasm of connective and soft tissue, upper arm
57482	B311200	Malignant neoplasm of connective and soft tissue of fore-arm
19321	B311300	Malignant neoplasm of connective and soft tissue of hand
91586	B311400	Malignant neoplasm of connective and soft tissue of finger
63988	B311500	Malignant neoplasm of connective and soft tissue of thumb
66088	B312.00	Malig neop of connective and soft tissue of hip and leg

102949	B312000	Malignant neoplasm of connective and soft tissue of hip
44805	B312100	Malig neop of connective and soft tissue thigh and upper leg
54965	B312200	Malig neop connective and soft tissue of popliteal space
30542	B312300	Malig neop of connective and soft tissue of lower leg
54222	B312400	Malignant neoplasm of connective and soft tissue of foot
99572	B312500	Malignant neoplasm of connective and soft tissue of toe
90546	B312z00	Malig neop connective and soft tissue hip and leg NOS
22290	B313.00	Malignant neoplasm of connective and soft tissue of thorax
29160	B313000	Malignant neoplasm of connective and soft tissue of axilla
54186	B313100	Malignant neoplasm of diaphragm
72522	B313200	Malignant neoplasm of great vessels
98408	B313z00	Malig neop of connective and soft tissue of thorax NOS
45071	B314.00	Malignant neoplasm of connective and soft tissue of abdomen
66488	B314000	Malig neop of connective and soft tissue of abdominal wall
94272	B314100	Malig neoplasm of connective and soft tissues of lumb spine
60247	B314z00	Malig neop of connective and soft tissue of abdomen NOS
51965	B315.00	Malignant neoplasm of connective and soft tissue of pelvis
70463	B315000	Malignant neoplasm of connective and soft tissue of buttock
67324	B315100	Malig neop of connective and soft tissue of inguinal region
59152	B315200	Malignant neoplasm of connective and soft tissue of perineum
58836	B315z00	Malig neop of connective and soft tissue of pelvis NOS
57471	B316.00	Malig neop of connective and soft tissue trunk unspecified
65233	B31y.00	Malig neop connective and soft tissue other specified site
15182	B31z.00	Malignant neoplasm of connective and soft tissue, site NOS
865	B32..00	Malignant melanoma of skin
70637	B320.00	Malignant melanoma of lip
54632	B321.00	Malignant melanoma of eyelid including canthus
57260	B322.00	Malignant melanoma of ear and external auricular canal
59061	B322000	Malignant melanoma of auricle (ear)
102145	B322100	Malignant melanoma of external auditory meatus
73744	B322z00	Malignant melanoma of ear and external auricular canal NOS
47252	B323.00	Malignant melanoma of other and unspecified parts of face
41278	B323000	Malignant melanoma of external surface of cheek
71136	B323100	Malignant melanoma of chin
47094	B323200	Malignant melanoma of eyebrow
68133	B323300	Malignant melanoma of forehead
45139	B323400	Malignant melanoma of external surface of nose
58958	B323500	Malignant melanoma of temple
67806	B323z00	Malignant melanoma of face NOS
65625	B324.00	Malignant melanoma of scalp and neck
55881	B324000	Malignant melanoma of scalp
45306	B324100	Malignant melanoma of neck
99257	B324z00	Malignant melanoma of scalp and neck NOS
38689	B325.00	Malignant melanoma of trunk (excluding scrotum)
49814	B325000	Malignant melanoma of axilla

32768	B325100	Malignant melanoma of breast
53629	B325200	Malignant melanoma of buttock
34259	B325300	Malignant melanoma of groin
95629	B325500	Malignant melanoma of perineum
43715	B325600	Malignant melanoma of umbilicus
43463	B325700	Malignant melanoma of back
51209	B325800	Malignant melanoma of chest wall
45760	B325z00	Malignant melanoma of trunk, excluding scrotum, NOS
65164	B326.00	Malignant melanoma of upper limb and shoulder
50505	B326000	Malignant melanoma of shoulder
54685	B326100	Malignant melanoma of upper arm
45755	B326200	Malignant melanoma of fore-arm
62475	B326300	Malignant melanoma of hand
25602	B326400	Malignant melanoma of finger
63997	B326500	Malignant melanoma of thumb
55292	B326z00	Malignant melanoma of upper limb or shoulder NOS
46255	B327.00	Malignant melanoma of lower limb and hip
73536	B327000	Malignant melanoma of hip
51873	B327100	Malignant melanoma of thigh
54305	B327200	Malignant melanoma of knee
39878	B327300	Malignant melanoma of popliteal fossa area
37872	B327400	Malignant melanoma of lower leg
42714	B327500	Malignant melanoma of ankle
61246	B327600	Malignant melanoma of heel
41490	B327700	Malignant melanoma of foot
36899	B327800	Malignant melanoma of toe
53369	B327900	Malignant melanoma of great toe
64327	B327z00	Malignant melanoma of lower limb or hip NOS
42153	B32y.00	Malignant melanoma of other specified skin site
96585	B32y000	Overlapping malignant melanoma of skin
28556	B32z.00	Malignant melanoma of skin NOS
3968	B34..00	Malignant neoplasm of female breast
348	B34..11	Ca female breast
26853	B340.00	Malignant neoplasm of nipple and areola of female breast
23380	B340000	Malignant neoplasm of nipple of female breast
64686	B340100	Malignant neoplasm of areola of female breast
59831	B340z00	Malignant neoplasm of nipple or areola of female breast NOS
31546	B341.00	Malignant neoplasm of central part of female breast
29826	B342.00	Malignant neoplasm of upper-inner quadrant of female breast
45222	B343.00	Malignant neoplasm of lower-inner quadrant of female breast
23399	B344.00	Malignant neoplasm of upper-outer quadrant of female breast
42070	B345.00	Malignant neoplasm of lower-outer quadrant of female breast
20685	B346.00	Malignant neoplasm of axillary tail of female breast
49148	B347.00	Malignant neoplasm, overlapping lesion of breast
56715	B34y.00	Malignant neoplasm of other site of female breast

95057	B34y000	Malignant neoplasm of ectopic site of female breast
38475	B34yz00	Malignant neoplasm of other site of female breast NOS
9470	B34z.00	Malignant neoplasm of female breast NOS
19423	B35..00	Malignant neoplasm of male breast
54494	B350.00	Malignant neoplasm of nipple and areola of male breast
68480	B350000	Malignant neoplasm of nipple of male breast
67884	B350100	Malignant neoplasm of areola of male breast
54202	B35z.00	Malignant neoplasm of other site of male breast
95323	B35z000	Malignant neoplasm of ectopic site of male breast
48809	B35zz00	Malignant neoplasm of male breast NOS
19389	B3y..00	Malig neop of bone, connective tissue, skin and breast OS
41011	B3z..00	Malig neop of bone, connective tissue, skin and breast NOS
13252	B4...00	Malignant neoplasm of genitourinary organ
16874	B4...11	Carcinoma of genitourinary organ
2744	B40..00	Malignant neoplasm of uterus, part unspecified
2747	B41..00	Malignant neoplasm of cervix uteri
3230	B41..11	Cervical carcinoma (uterus)
48820	B410.00	Malignant neoplasm of endocervix
57235	B410000	Malignant neoplasm of endocervical canal
53103	B410100	Malignant neoplasm of endocervical gland
50285	B410z00	Malignant neoplasm of endocervix NOS
50297	B411.00	Malignant neoplasm of exocervix
58094	B412.00	Malignant neoplasm, overlapping lesion of cervix uteri
32955	B41y.00	Malignant neoplasm of other site of cervix
95505	B41y000	Malignant neoplasm of cervical stump
57719	B41y100	Malignant neoplasm of squamocolumnar junction of cervix
43435	B41yz00	Malignant neoplasm of other site of cervix NOS
28311	B41z.00	Malignant neoplasm of cervix uteri NOS
93762	B42..00	Malignant neoplasm of placenta
28003	B420.00	Choriocarcinoma
7046	B43..00	Malignant neoplasm of body of uterus
3213	B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
72723	B430000	Malignant neoplasm of cornu of corpus uteri
68155	B430100	Malignant neoplasm of fundus of corpus uteri
2890	B430200	Malignant neoplasm of endometrium of corpus uteri
49400	B430211	Malignant neoplasm of endometrium
45793	B430300	Malignant neoplasm of myometrium of corpus uteri
45490	B430z00	Malignant neoplasm of corpus uteri NOS
43940	B431.00	Malignant neoplasm of isthmus of uterine body
59097	B431000	Malignant neoplasm of lower uterine segment
70729	B431z00	Malignant neoplasm of isthmus of uterine body NOS
16967	B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
31608	B43y.00	Malignant neoplasm of other site of uterine body
33617	B43z.00	Malignant neoplasm of body of uterus NOS
19141	B44..00	Malignant neoplasm of ovary and other uterine adnexa

7805	B440.00	Malignant neoplasm of ovary
1986	B440.11	Cancer of ovary
49828	B441.00	Malignant neoplasm of fallopian tube
101778	B442.00	Malignant neoplasm of broad ligament
46153	B443.00	Malignant neoplasm of parametrium
97996	B44y.00	Malignant neoplasm of other site of uterine adnexa
65106	B44z.00	Malignant neoplasm of uterine adnexa NOS
4555	B45..00	Malig neop of other and unspecified female genital organs
37328	B450.00	Malignant neoplasm of vagina
10698	B450100	Malignant neoplasm of vaginal vault
60772	B450z00	Malignant neoplasm of vagina NOS
43761	B451.00	Malignant neoplasm of labia majora
47899	B451000	Malignant neoplasm of greater vestibular (Bartholin's) gland
59362	B451z00	Malignant neoplasm of labia majora NOS
58061	B452.00	Malignant neoplasm of labia minora
53910	B453.00	Malignant neoplasm of clitoris
4554	B454.00	Malignant neoplasm of vulva unspecified
11991	B454.11	Primary vulval cancer
26454	B45X.00	Malignant neoplasm/overlapping lesion/feml genital organs
95421	B45y.00	Malignant neoplasm of other specified female genital organ
27617	B45y000	Malignant neoplasm of overlapping lesion of vulva
20166	B45z.00	Malignant neoplasm of female genital organ NOS
780	B46..00	Malignant neoplasm of prostate
15148	B47..00	Malignant neoplasm of testis
64602	B470.00	Malignant neoplasm of undescended testis
7740	B470200	Seminoma of undescended testis
36325	B470300	Teratoma of undescended testis
96429	B470z00	Malignant neoplasm of undescended testis NOS
19475	B471.00	Malignant neoplasm of descended testis
21786	B471000	Seminoma of descended testis
9476	B471100	Teratoma of descended testis
91509	B471z00	Malignant neoplasm of descended testis NOS
38510	B47z.00	Malignant neoplasm of testis NOS
2961	B47z.11	Seminoma of testis
15989	B47z.12	Teratoma of testis
3541	B48..00	Malignant neoplasm of penis and other male genital organs
50681	B480.00	Malignant neoplasm of prepuce (foreskin)
17841	B481.00	Malignant neoplasm of glans penis
48743	B482.00	Malignant neoplasm of body of penis
43392	B483.00	Malignant neoplasm of penis, part unspecified
72127	B484.00	Malignant neoplasm of epididymis
63331	B485.00	Malignant neoplasm of spermatic cord
47767	B486.00	Malignant neoplasm of scrotum
52570	B487.00	Malignant neoplasm, overlapping lesion of penis
67949	B48y.00	Malignant neoplasm of other male genital organ

68161	B48y000	Malignant neoplasm of seminal vesicle
47668	B48y100	Malignant neoplasm of tunica vaginalis
68824	B48y200	Malignant neoplasm, overlapping lesion male genital orgs
92329	B48yz00	Malignant neoplasm of other male genital organ NOS
63224	B48z.00	Malignant neoplasm of penis and other male genital organ NOS
779	B49..00	Malignant neoplasm of urinary bladder
38862	B490.00	Malignant neoplasm of trigone of urinary bladder
44996	B491.00	Malignant neoplasm of dome of urinary bladder
35963	B492.00	Malignant neoplasm of lateral wall of urinary bladder
19162	B493.00	Malignant neoplasm of anterior wall of urinary bladder
42012	B494.00	Malignant neoplasm of posterior wall of urinary bladder
41571	B495.00	Malignant neoplasm of bladder neck
28241	B496.00	Malignant neoplasm of ureteric orifice
42023	B497.00	Malignant neoplasm of urachus
36949	B49y.00	Malignant neoplasm of other site of urinary bladder
47801	B49y000	Malignant neoplasm, overlapping lesion of bladder
31102	B49z.00	Malignant neoplasm of urinary bladder NOS
13559	B4A..00	Malig neop of kidney and other unspecified urinary organs
18712	B4A..11	Renal malignant neoplasm
1599	B4A0.00	Malignant neoplasm of kidney parenchyma
7978	B4A0000	Hypernephroma
12389	B4A1.00	Malignant neoplasm of renal pelvis
27540	B4A1000	Malignant neoplasm of renal calyces
101608	B4A1100	Malignant neoplasm of ureteropelvic junction
54184	B4A1z00	Malignant neoplasm of renal pelvis NOS
15223	B4A2.00	Malignant neoplasm of ureter
15644	B4A3.00	Malignant neoplasm of urethra
72174	B4A4.00	Malignant neoplasm of paraurethral glands
44884	B4Ay.00	Malignant neoplasm of other urinary organs
59286	B4Ay000	Malignant neoplasm of overlapping lesion of urinary organs
29462	B4Az.00	Malignant neoplasm of kidney or urinary organs NOS
38931	B4y..00	Malignant neoplasm of genitourinary organ OS
52594	B4z..00	Malignant neoplasm of genitourinary organ NOS
10995	B5...00	Malignant neoplasm of other and unspecified sites
8693	B5...11	Carcinoma of other and unspecified sites
20160	B50..00	Malignant neoplasm of eye
98813	B500.00	Malig neop eyeball excl conjunctiva, cornea, retina, choroid
59041	B500000	Malignant neoplasm of ciliary body
59381	B500100	Malignant neoplasm of iris
56718	B500z00	Malignant neoplasm of eyeball NOS
45667	B501.00	Malignant neoplasm of orbit
86996	B501000	Malignant neoplasm of connective tissue of orbit
63104	B501z00	Malignant neoplasm of orbit NOS
64817	B502.00	Malignant neoplasm of lacrimal gland
63657	B503.00	Malignant neoplasm of conjunctiva

73992	B504.00	Malignant neoplasm of cornea
28069	B505.00	Malignant neoplasm of retina
15991	B506.00	Malignant neoplasm of choroid
71584	B507.00	Malignant neoplasm of lacrimal duct
101805	B507000	Malignant neoplasm of lacrimal sac
65357	B507100	Malignant neoplasm of nasolacrimal duct
45922	B508.00	Malignant neoplasm, overlapping lesion of eye and adnexa
40437	B50y.00	Malignant neoplasm of other specified site of eye
54956	B50z.00	Malignant neoplasm of eye NOS
18617	B51..00	Malignant neoplasm of brain
10851	B51..11	Cerebral tumour - malignant
15711	B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)
48073	B510000	Malignant neoplasm of basal ganglia
61399	B510100	Malignant neoplasm of cerebral cortex
99913	B510300	Malignant neoplasm of globus pallidus
70942	B510400	Malignant neoplasm of hypothalamus
62126	B510500	Malignant neoplasm of thalamus
54133	B510z00	Malignant neoplasm of cerebrum NOS
42426	B511.00	Malignant neoplasm of frontal lobe
46792	B512.00	Malignant neoplasm of temporal lobe
67236	B512000	Malignant neoplasm of hippocampus
47556	B512z00	Malignant neoplasm of temporal lobe NOS
19226	B513.00	Malignant neoplasm of parietal lobe
39088	B514.00	Malignant neoplasm of occipital lobe
52511	B515.00	Malignant neoplasm of cerebral ventricles
46789	B515000	Malignant neoplasm of choroid plexus
45154	B516.00	Malignant neoplasm of cerebellum
44089	B517.00	Malignant neoplasm of brain stem
64557	B517000	Malignant neoplasm of cerebral peduncle
49132	B517100	Malignant neoplasm of medulla oblongata
93537	B517200	Malignant neoplasm of midbrain
91240	B517300	Malignant neoplasm of pons
68641	B517z00	Malignant neoplasm of brain stem NOS
71139	B51y.00	Malignant neoplasm of other parts of brain
59170	B51y000	Malignant neoplasm of corpus callosum
65241	B51y200	Malignant neoplasm, overlapping lesion of brain
100733	B51yz00	Malignant neoplasm of other part of brain NOS
41520	B51z.00	Malignant neoplasm of brain NOS
65458	B52..00	Malig neop of other and unspecified parts of nervous system
99621	B520.00	Malignant neoplasm of cranial nerves
64971	B520000	Malignant neoplasm of olfactory bulb
70126	B520100	Malignant neoplasm of optic nerve
65599	B520200	Malignant neoplasm of acoustic nerve
101086	B520z00	Malignant neoplasm of cranial nerves NOS
28919	B521.00	Malignant neoplasm of cerebral meninges

70104	B521z00	Malignant neoplasm of cerebral meninges NOS
51115	B522.00	Malignant neoplasm of spinal cord
49714	B523.00	Malignant neoplasm of spinal meninges
67211	B523z00	Malignant neoplasm of spinal meninges NOS
24235	B524.00	Malig neopl peripheral nerves and autonomic nervous system
63568	B524000	Malignant neoplasm of peripheral nerves of head, face & neck
61716	B524100	Malignant neoplasm of peripheral nerve,upp limb,incl should
89258	B524200	Malignant neoplasm of peripheral nerve of low limb, incl hip
63695	B524300	Malignant neoplasm of peripheral nerve of thorax
86046	B524400	Malignant neoplasm of peripheral nerve of abdomen
73988	B524500	Malignant neoplasm of peripheral nerve of pelvis
50777	B524600	Malignant neoplasm,overlap lesion periph nerve & auton ns
9622	B525.00	Malignant neoplasm of cauda equina
53504	B52W.00	Malig neopl, overlap lesion brain & other part of CNS
49875	B52X.00	Malignant neoplasm of meninges, unspecified
88144	B52y.00	Malignant neoplasm of other specified part of nervous system
56490	B52z.00	Malignant neoplasm of nervous system NOS
5637	B53..00	Malignant neoplasm of thyroid gland
30511	B54..00	Malig neop of other endocrine glands and related structures
28148	B540.00	Malignant neoplasm of adrenal gland
18231	B540.11	Phaeochromocytoma
61390	B540000	Malignant neoplasm of adrenal cortex
94220	B540100	Malignant neoplasm of adrenal medulla
70824	B540z00	Malignant neoplasm of adrenal gland NOS
4218	B541.00	Malignant neoplasm of parathyroid gland
59823	B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
8550	B542000	Malignant neoplasm of pituitary gland
39899	B542100	Malignant neoplasm of craniopharyngeal duct
59718	B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS
42460	B543.00	Malignant neoplasm of pineal gland
57047	B544.00	Malignant neoplasm of carotid body
50035	B545.00	Malignant neoplasm of aortic body and other paraganglia
51795	B545000	Malignant neoplasm of glomus jugulare
47840	B545100	Malignant neoplasm of aortic body
46905	B545200	Malignant neoplasm of coccygeal body
87113	B54X.00	Malignant neoplasm-pluriglandular involvement,unspecified
90659	B54y.00	Malignant neoplasm of other specified endocrine gland
64195	B54z.00	Malig neop of endocrine gland or related structure NOS
9030	B55..00	Malignant neoplasm of other and ill-defined sites
68236	B550.00	Malignant neoplasm of head, neck and face
55098	B550000	Malignant neoplasm of head NOS
41931	B550100	Malignant neoplasm of cheek NOS
12490	B550200	Malignant neoplasm of nose NOS
51818	B550300	Malignant neoplasm of jaw NOS
16280	B550400	Malignant neoplasm of neck NOS

73510	B550500	Malignant neoplasm of supraclavicular fossa NOS
58903	B550z00	Malignant neoplasm of head, neck and face NOS
47286	B551.00	Malignant neoplasm of thorax
37618	B551000	Malignant neoplasm of axilla NOS
23861	B551100	Malignant neoplasm of chest wall NOS
97547	B551200	Malignant neoplasm of intrathoracic site NOS
64810	B551z00	Malignant neoplasm of thorax NOS
15976	B552.00	Malignant neoplasm of abdomen
52316	B553.00	Malignant neoplasm of pelvis
57854	B553000	Malignant neoplasm of inguinal region NOS
89916	B553100	Malignant neoplasm of presacral region
55101	B553z00	Malignant neoplasm of pelvis NOS
27449	B554.00	Malignant neoplasm of upper limb NOS
31399	B555.00	Malignant neoplasm of lower limb NOS
42218	B55y.00	Malignant neoplasm of other specified sites
68787	B55y000	Malignant neoplasm of back NOS
67217	B55y100	Malignant neoplasm of trunk NOS
94355	B55y200	Malignant neoplasm of flank NOS
60052	B55yz00	Malignant neoplasm of specified site NOS
45267	B55z.00	Malignant neoplasm of other and ill defined site NOS
9618	B56..00	Secondary and unspecified malignant neoplasm of lymph nodes
7830	B56..11	Lymph node metastases
49214	B560.00	Secondary and unspec malig neop lymph nodes head/face/neck
64918	B560000	Secondary and unspec malig neop of superficial parotid LN
66775	B560100	Secondary and unspec malignant neoplasm mastoid lymph nodes
33395	B560200	Secondary and unspec malig neop superficial cervical LN
65253	B560300	Secondary and unspec malignant neoplasm occipital lymph node
92703	B560400	Secondary and unspec malig neop deep parotid lymph nodes
39433	B560500	Secondary and unspec malig neop submandibular lymph nodes
28059	B560600	Secondary and unspec malig neop of facial lymph nodes
38343	B560700	Secondary and unspec malig neop submental lymph nodes
44627	B560800	Secondary and unspec malig neop anterior cervical LN
68611	B560900	Secondary and unspec malig neop deep cervical LN
67129	B560z00	Secondary unspec malig neop lymph nodes head/face/neck NOS
64116	B561.00	Secondary and unspec malig neop intrathoracic lymph nodes
37919	B561000	Secondary and unspec malig neop internal mammary lymph nodes
95378	B561200	Secondary and unspec malig neop diaphragmatic lymph nodes
25366	B561300	Secondary and unspec malig neop ant mediastinal lymph nodes
55463	B561400	Secondary and unspec malig neop post mediastinal lymph nodes
58692	B561500	Secondary and unspec malig neop paratracheal lymph nodes
67797	B561600	Secondary and unspec malig neop superfic tracheobronchial LN
69392	B561700	Secondary and unspec malig neop inferior tracheobronchial LN
62124	B561800	Secondary and unspec malig neop bronchopulmonary lymph nodes
52190	B561900	Secondary and unspec malig neop pulmonary lymph nodes
93716	B561z00	Secondary and unspec malig neop intrathoracic LN NOS

52736	B562.00	Secondary and unspec malig neop intra-abdominal lymph nodes
41691	B562000	Secondary and unspec malig neop coeliac lymph nodes
72713	B562100	Secondary and unspec malig neop superficial mesenteric LN
61677	B562200	Secondary and unspec malig neop inferior mesenteric LN
18658	B562300	Secondary and unspec malig neop common iliac lymph nodes
69132	B562400	Secondary and unspec malig neop external iliac lymph nodes
44931	B562z00	Secondary and unspec malig neop intra-abdominal LN NOS
50199	B563.00	Secondary and unspec malig neop axilla and upper limb LN
37540	B563000	Secondary and unspec malig neop axillary lymph nodes
98626	B563100	Secondary and unspec malig neop supratrochlear lymph nodes
50904	B563200	Secondary and unspec malig neop infraclavicular lymph nodes
46409	B563300	Secondary and unspec malig neop pectoral lymph nodes
73538	B563z00	Secondary and unspec malig neop axilla and upper limb LN NOS
63915	B564.00	Secondary and unspec malig neop inguinal and lower limb LN
54278	B564000	Secondary and unspec malig neop superficial inguinal LN
61289	B564100	Secondary and unspec malig neop deep inguinal lymph nodes
70747	B564z00	Secondary and unspec malig neop of inguinal and leg LN NOS
6701	B565.00	Secondary and unspec malig neop intrapelvic lymph nodes
84368	B565000	Secondary and unspec malig neop internal iliac lymph nodes
101662	B565200	Secondary and unspec malig neop circumflex iliac LN
47366	B565300	Secondary and unspec malig neop sacral lymph nodes
72803	B565z00	Secondary and unspec malig neop intrapelvic LN NOS
20159	B56y.00	Secondary and unspec malig neop lymph nodes multiple sites
15507	B56z.00	Secondary and unspec malig neop lymph nodes NOS
35053	B57..00	Secondary malig neop of respiratory and digestive systems
6471	B57..11	Metastases of respiratory and/or digestive systems
24301	B57..12	Secondary carcinoma of respiratory and/or digestive systems
4137	B570.00	Secondary malignant neoplasm of lung
51551	B571.00	Secondary malignant neoplasm of mediastinum
16213	B572.00	Secondary malignant neoplasm of pleura
62584	B573.00	Secondary malignant neoplasm of other respiratory organs
64680	B574.00	Secondary malignant neoplasm of small intestine and duodenum
55946	B574000	Secondary malignant neoplasm of duodenum
99511	B574200	Secondary malignant neoplasm of ileum
70026	B574z00	Secondary malig neop of small intestine or duodenum NOS
44529	B575.00	Secondary malignant neoplasm of large intestine and rectum
28727	B575000	Secondary malignant neoplasm of colon
62909	B575100	Secondary malignant neoplasm of rectum
36200	B575z00	Secondary malig neop of large intestine or rectum NOS
67396	B576.00	Secondary malig neop of retroperitoneum and peritoneum
35364	B576000	Secondary malignant neoplasm of retroperitoneum
27391	B576100	Secondary malignant neoplasm of peritoneum
8154	B576200	Malignant ascites
97672	B576z00	Secondary malig neop of retroperitoneum or peritoneum NOS
15103	B577.00	Secondary malignant neoplasm of liver

4403	B577.11	Liver metastases
56345	B57y.00	Secondary malignant neoplasm of other digestive organ
66083	B57z.00	Secondary malig neop of respiratory or digestive system NOS
5842	B58..00	Secondary malignant neoplasm of other specified sites
27651	B58..11	Secondary carcinoma of other specified sites
1952	B580.00	Secondary malignant neoplasm of kidney
73213	B581.00	Secondary malignant neoplasm of other urinary organs
60134	B581000	Secondary malignant neoplasm of ureter
22146	B581100	Secondary malignant neoplasm of bladder
53528	B581200	Secondary malignant neoplasm of urethra
62828	B581z00	Secondary malignant neoplasm of other urinary organ NOS
19945	B582.00	Secondary malignant neoplasm of skin
43930	B582000	Secondary malignant neoplasm of skin of head
100296	B582100	Secondary malignant neoplasm of skin of face
35999	B582200	Secondary malignant neoplasm of skin of neck
41144	B582300	Secondary malignant neoplasm of skin of trunk
63896	B582400	Secondary malignant neoplasm of skin of shoulder and arm
48828	B582500	Secondary malignant neoplasm of skin of hip and leg
9505	B582600	Secondary malignant neoplasm of skin of breast
55096	B582z00	Secondary malignant neoplasm of skin NOS
33843	B583.00	Secondary malignant neoplasm of brain and spinal cord
5198	B583000	Secondary malignant neoplasm of brain
38918	B583100	Secondary malignant neoplasm of spinal cord
5199	B583200	Cerebral metastasis
59375	B583z00	Secondary malignant neoplasm of brain or spinal cord NOS
54120	B584.00	Secondary malignant neoplasm of other part of nervous system
7654	B585.00	Secondary malignant neoplasm of bone and bone marrow
18676	B585000	Pathological fracture due to metastatic bone disease
44615	B586.00	Secondary malignant neoplasm of ovary
36401	B587.00	Secondary malignant neoplasm of adrenal gland
18616	B58y.00	Secondary malignant neoplasm of other specified sites
16760	B58y000	Secondary malignant neoplasm of breast
55090	B58y100	Secondary malignant neoplasm of uterus
73616	B58y200	Secondary malignant neoplasm of cervix uteri
97832	B58y211	Secondary cancer of the cervix
70736	B58y300	Secondary malignant neoplasm of vagina
60335	B58y400	Secondary malignant neoplasm of vulva
65490	B58y411	Secondary cancer of the vulva
21590	B58y500	Secondary malignant neoplasm of prostate
34145	B58y600	Secondary malignant neoplasm of testis
49145	B58y700	Secondary malignant neoplasm of penis
45824	B58y900	Secondary malignant neoplasm of tongue
22524	B58yz00	Secondary malignant neoplasm of other specified site NOS
16500	B58z.00	Secondary malignant neoplasm of other specified site NOS
47810	B59..00	Malignant neoplasm of unspecified site

13569	B590.00	Disseminated malignancy NOS
6170	B590.11	Carcinomatosis
26034	B591.00	Other malignant neoplasm NOS
51352	B592.00	Malignant neoplasms of independent (primary) multiple sites
65466	B592X00	Kaposi's sarcoma of multiple organs
11035	B593.00	Primary malignant neoplasm of unknown site
54679	B594.00	Secondary malignant neoplasm of unknown site
54267	B59z.00	Malignant neoplasm of unspecified site NOS
49525	B59zX00	Kaposi's sarcoma, unspecified
38736	B5y..00	Malignant neoplasm of other and unspecified site OS
1056	B5z..00	Malignant neoplasm of other and unspecified site NOS
12323	B6...00	Malignant neoplasm of lymphatic and haemopoietic tissue
37112	B6...11	Malignant neoplasm of histiocytic tissue
41369	B60..00	Lymphosarcoma and reticulosarcoma
1481	B600.00	Reticulosarcoma
60242	B600000	Reticulosarcoma of unspecified site
71031	B600100	Reticulosarcoma of lymph nodes of head, face and neck
70374	B600300	Reticulosarcoma of intra-abdominal lymph nodes
95058	B600700	Reticulosarcoma of spleen
99240	B600z00	Reticulosarcoma NOS
27416	B601.00	Lymphosarcoma
71625	B601000	Lymphosarcoma of unspecified site
71238	B601100	Lymphosarcoma of lymph nodes of head, face and neck
62380	B601200	Lymphosarcoma of intrathoracic lymph nodes
64670	B601300	Lymphosarcoma of intra-abdominal lymph nodes
100352	B601500	Lymphosarcoma of lymph nodes of inguinal region and leg
103245	B601700	Lymphosarcoma of spleen
63723	B601z00	Lymphosarcoma NOS
21402	B602.00	Burkitt's lymphoma
59115	B602100	Burkitt's lymphoma of lymph nodes of head, face and neck
100006	B602200	Burkitt's lymphoma of intrathoracic lymph nodes
97577	B602300	Burkitt's lymphoma of intra-abdominal lymph nodes
92380	B602500	Burkitt's lymphoma of lymph nodes of inguinal region and leg
71304	B602z00	Burkitt's lymphoma NOS
99887	B60y.00	Other specified reticulosarcoma or lymphosarcoma
99951	B60z.00	Reticulosarcoma or lymphosarcoma NOS
2462	B61..00	Hodgkin's disease
65489	B610.00	Hodgkin's paragranuloma
100423	B610100	Hodgkin's paragranuloma of lymph nodes of head, face, neck
98840	B610300	Hodgkin's paragranuloma of intra-abdominal lymph nodes
44196	B611.00	Hodgkin's granuloma
98909	B611100	Hodgkin's granuloma of lymph nodes of head, face and neck
64036	B612.00	Hodgkin's sarcoma
68039	B612400	Hodgkin's sarcoma of lymph nodes of axilla and upper limb
38939	B613.00	Hodgkin's disease, lymphocytic-histiocytic predominance

71142	B613000	Hodgkin's, lymphocytic-histiocytic predominance unspec site
68330	B613100	Hodgkin's, lymphocytic-histiocytic pred of head, face, neck
92245	B613200	Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes
73532	B613300	Hodgkin's, lymphocytic-histiocytic pred intra-abdominal node
93951	B613500	Hodgkin's, lymphocytic-histiocytic pred inguinal and leg
95338	B613600	Hodgkin's, lymphocytic-histiocytic pred intrapelvic nodes
29876	B613z00	Hodgkin's, lymphocytic-histiocytic predominance NOS
29178	B614.00	Hodgkin's disease, nodular sclerosis
57225	B614000	Hodgkin's disease, nodular sclerosis of unspecified site
55303	B614100	Hodgkin's nodular sclerosis of head, face and neck
67506	B614200	Hodgkin's nodular sclerosis of intrathoracic lymph nodes
61149	B614300	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes
65483	B614400	Hodgkin's nodular sclerosis of lymph nodes of axilla and arm
19140	B614800	Hodgkin's nodular sclerosis of lymph nodes of multiple sites
63054	B614z00	Hodgkin's disease, nodular sclerosis NOS
49605	B615.00	Hodgkin's disease, mixed cellularity
97863	B615000	Hodgkin's disease, mixed cellularity of unspecified site
94407	B615100	Hodgkin's mixed cellularity of lymph nodes head, face, neck
58684	B615200	Hodgkin's mixed cellularity of intrathoracic lymph nodes
94005	B615z00	Hodgkin's disease, mixed cellularity NOS
67703	B616.00	Hodgkin's disease, lymphocytic depletion
95049	B616000	Hodgkin's lymphocytic depletion of unspecified site
63625	B616400	Hodgkin's lymphocytic depletion lymph nodes axilla and arm
101715	B616700	Hodgkin's disease, lymphocytic depletion of spleen
101530	B616z00	Hodgkin's disease, lymphocytic depletion NOS
53397	B61z.00	Hodgkin's disease NOS
61662	B61z000	Hodgkin's disease NOS, unspecified site
59778	B61z100	Hodgkin's disease NOS of lymph nodes of head, face and neck
59755	B61z200	Hodgkin's disease NOS of intrathoracic lymph nodes
91900	B61z400	Hodgkin's disease NOS of lymph nodes of axilla and arm
99012	B61z500	Hodgkin's disease NOS of lymph nodes inguinal region and leg
94279	B61z700	Hodgkin's disease NOS of spleen
97746	B61z800	Hodgkin's disease NOS of lymph nodes of multiple sites
42461	B61zz00	Hodgkin's disease NOS
33333	B62..00	Other malignant neoplasm of lymphoid and histiocytic tissue
5179	B620.00	Nodular lymphoma (Brill - Symmers disease)
66327	B620000	Nodular lymphoma of unspecified site
45264	B620100	Nodular lymphoma of lymph nodes of head, face and neck
92068	B620300	Nodular lymphoma of intra-abdominal lymph nodes
94995	B620500	Nodular lymphoma of lymph nodes of inguinal region and leg
58082	B620800	Nodular lymphoma of lymph nodes of multiple sites
65701	B620z00	Nodular lymphoma NOS
12006	B621.00	Mycosis fungoides
95949	B621000	Mycosis fungoides of unspecified site
91674	B621300	Mycosis fungoides of intra-abdominal lymph nodes

96379	B621400	Mycosis fungoides of lymph nodes of axilla and upper limb
72714	B621500	Mycosis fungoides of lymph nodes of inguinal region and leg
95012	B621800	Mycosis fungoides of lymph nodes of multiple sites
38005	B621z00	Mycosis fungoides NOS
35014	B622.00	Sezary's disease
100532	B622z00	Sezary's disease NOS
44267	B623.00	Malignant histiocytosis
69497	B623000	Malignant histiocytosis of unspecified site
94415	B623100	Malignant histiocytosis of lymph nodes head, face and neck
65642	B623300	Malignant histiocytosis of intra-abdominal lymph nodes
58871	B623z00	Malignant histiocytosis NOS
27330	B624.00	Leukaemic reticuloendotheliosis
5137	B624.11	Leukaemic reticuloendotheliosis
87335	B624.12	Hairy cell leukaemia
65122	B624000	Leukaemic reticuloendotheliosis of unspecified sites
65123	B624300	Leukaemic reticuloend of intra-abdominal lymph nodes
73777	B624z00	Leukaemic reticuloendotheliosis NOS
34926	B625.00	Letterer-Siwe disease
4870	B625.11	Histiocytosis X (acute, progressive)
102715	B625000	Letterer-Siwe disease of unspecified sites
102158	B625200	Letterer-Siwe disease of intrathoracic lymph nodes
54083	B625800	Letterer-Siwe disease of lymph nodes of multiple sites
47204	B625z00	Letterer-Siwe disease NOS
15036	B626.00	Malignant mast cell tumours
103900	B626000	Mast cell malignancy of unspecified site
100615	B626500	Mast cell malignancy of lymph nodes inguinal region and leg
31324	B626800	Mast cell malignancy of lymph nodes of multple sites
89657	B626z00	Malignant mast cell tumour NOS
3604	B627.00	Non - Hodgkin's lymphoma
28639	B627000	Follicular non-Hodgkin's small cleaved cell lymphoma
70842	B627100	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma
49262	B627200	Follicular non-Hodgkin's large cell lymphoma
50668	B627300	Diffuse non-Hodgkin's small cell (diffuse) lymphoma
50695	B627500	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
53551	B627600	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
17460	B627700	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
65180	B627800	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
95715	B627900	Mucosa-associated lymphoma
95545	B627911	Maltoma
101114	B627A00	Diffuse non-Hodgkin's large cell lymphoma
31576	B627B00	Other types of follicular non-Hodgkin's lymphoma
21549	B627C00	Follicular non-Hodgkin's lymphoma
17182	B627C11	Follicular lymphoma NOS
70509	B627D00	Diffuse non-Hodgkin's centroblastic lymphoma
102594	B627E00	Diffuse large B-cell lymphoma

31794	B627W00	Unspecified B-cell non-Hodgkin's lymphoma
39798	B627X00	Diffuse non-Hodgkin's lymphoma, unspecified
17887	B62x.00	Malignant lymphoma otherwise specified
90201	B62x000	T-zone lymphoma
57737	B62x100	Lymphoepithelioid lymphoma
12464	B62x200	Peripheral T-cell lymphoma
62437	B62x400	Malignant reticulosis
58962	B62x500	Malignant immunoproliferative small intestinal disease
95630	B62x600	True histiocytic lymphoma
44318	B62xX00	Oth and unspecif peripheral & cutaneous T-cell lymphomas
12335	B62y.00	Malignant lymphoma NOS
57427	B62y000	Malignant lymphoma NOS of unspecified site
50696	B62y100	Malignant lymphoma NOS of lymph nodes of head, face and neck
72725	B62y200	Malignant lymphoma NOS of intrathoracic lymph nodes
42579	B62y300	Malignant lymphoma NOS of intra-abdominal lymph nodes
34089	B62y400	Malignant lymphoma NOS of lymph nodes of axilla and arm
63105	B62y500	Malignant lymphoma NOS of lymph node inguinal region and leg
71262	B62y600	Malignant lymphoma NOS of intrapelvic lymph nodes
60092	B62y700	Malignant lymphoma NOS of spleen
15504	B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites
15027	B62yz00	Malignant lymphoma NOS
65434	B62z.00	Malignant neoplasms of lymphoid and histiocytic tissue NOS
64427	B62z100	Unspec malig neop lymphoid/histiocytic lymph node head/neck
93384	B62z200	Unspec malig neop lymphoid/histiocytic of intrathoracic node
103353	B62z300	Unspec malig neop lymphoid/histiocytic intra-abdominal nodes
71609	B62z500	Unspec malig neop lymphoid/histiocytic nodes inguinal/leg
101465	B62z800	Unspec malig neop lymphoid/histiocytic of multiple sites
95792	B62zz00	Lymphoid and histiocytic malignancy NOS
70716	B62zz11	Immunoproliferative neoplasm
37182	B63..00	Multiple myeloma and immunoproliferative neoplasms
4944	B630.00	Multiple myeloma
43552	B630.11	Kahler's disease
15211	B630.12	Myelomatosis
22158	B630000	Malignant plasma cell neoplasm, extramedullary plasmacytoma
19028	B630100	Solitary myeloma
21329	B630200	Plasmacytoma NOS
46042	B630300	Lambda light chain myeloma
39187	B631.00	Plasma cell leukaemia
64567	B63y.00	Other immunoproliferative neoplasms
43450	B63z.00	Immunoproliferative neoplasm or myeloma NOS
19372	B64..00	Lymphoid leukaemia
4222	B64..11	Lymphatic leukaemia
4251	B640.00	Acute lymphoid leukaemia
8625	B641.00	Chronic lymphoid leukaemia
27790	B641.11	Chronic lymphatic leukaemia

72774	B642.00	Subacute lymphoid leukaemia
49725	B64y.00	Other lymphoid leukaemia
31586	B64y100	Prolymphocytic leukaemia
37461	B64y200	Adult T-cell leukaemia
38331	B64yz00	Other lymphoid leukaemia NOS
38914	B64z.00	Lymphoid leukaemia NOS
7176	B65..00	Myeloid leukaemia
4413	B650.00	Acute myeloid leukaemia
10726	B651.00	Chronic myeloid leukaemia
31701	B651.11	Chronic granulocytic leukaemia
100786	B651000	Chronic eosinophilic leukaemia
102783	B651200	Chronic neutrophilic leukaemia
27520	B651z00	Chronic myeloid leukaemia NOS
63475	B652.00	Subacute myeloid leukaemia
70724	B653.00	Myeloid sarcoma
52327	B653000	Chloroma
39629	B653100	Granulocytic sarcoma
27664	B65y100	Acute promyelocytic leukaemia
66089	B65yz00	Other myeloid leukaemia NOS
33344	B65z.00	Myeloid leukaemia NOS
35875	B66..00	Monocytic leukaemia
67700	B66..12	Monoblastic leukaemia
19974	B660.00	Acute monocytic leukaemia
27458	B661.00	Chronic monocytic leukaemia
101606	B662.00	Subacute monocytic leukaemia
99015	B66y.00	Other monocytic leukaemia
103645	B66yz00	Other monocytic leukaemia NOS
93342	B66z.00	Monocytic leukaemia NOS
37272	B67..00	Other specified leukaemia
42539	B670.00	Acute erythraemia and erythroleukaemia
27340	B670.11	Di Guglielmo's disease
37468	B671.00	Chronic erythraemia
63653	B671.11	Heilmeyer - Schoner disease
57671	B672.00	Megakaryocytic leukaemia
65777	B672.11	Thrombocytic leukaemia
65721	B673.00	Mast cell leukaemia
50858	B674.00	Acute panmyelosis
28276	B675.00	Acute myelofibrosis
94174	B67y.00	Other and unspecified leukaemia
72197	B67y000	Lymphosarcoma cell leukaemia
99413	B67yz00	Other and unspecified leukaemia NOS
30632	B67z.00	Other specified leukaemia NOS
25191	B68..00	Leukaemia of unspecified cell type
4072	B680.00	Acute leukaemia NOS
16416	B681.00	Chronic leukaemia NOS

54793	B682.00	Subacute leukaemia NOS
34692	B68y.00	Other leukaemia of unspecified cell type
4250	B68z.00	Leukaemia NOS
20440	B69..00	Myelomonocytic leukaemia
61500	B690.00	Acute myelomonocytic leukaemia
22050	B691.00	Chronic myelomonocytic leukaemia
30646	B6y..00	Malignant neoplasm lymphatic or haematopoietic tissue OS
6115	B6y0.00	Myeloproliferative disorder
17056	B6y0.11	Myeloproliferative disease
39336	B6y1.00	Myelosclerosis with myeloid metaplasia
49301	B6z..00	Malignant neoplasm lymphatic or haematopoietic tissue NOS
50290	B6z0.00	Kaposi's sarcoma of lymph nodes
40592	Byu5.00	[X]Malignant neoplasm of mesothelial and soft tissue
67034	Byu5000	[X]Mesothelioma of other sites
21715	Byu5011	[X]Mesothelioma of lung
30526	Byu5100	[X]Mesothelioma, unspecified
93665	Byu5300	[X]Kaposi's sarcoma, unspecified
101668	Byu5400	[X]Malignant neoplasm/peripheral nerves of trunk,unspecified
95671	Byu5700	[X]Malignant neoplasm of peritoneum, unspecified
91896	Byu5800	[X]Mal neoplasm/connective+soft tissue of trunk,unspecified
91457	Byu5900	[X]Malignant neoplasm/connective + soft tissue,unspecified
60162	Byu5A00	[X]Malignant neoplasm overlapping lesion of skin
98361	Byu5B00	[X]Kaposi's sarcoma of other sites
12499	Byu6.00	[X]Malignant neoplasm of breast
40598	Byu7.00	[X]Malignant neoplasm of female genital organs
64497	Byu7000	[X]Malignant neoplasm of uterine adnexa, unspecified
57756	Byu7100	[X]Malignant neoplasm/other specified female genital organs
55588	Byu7300	[X]Malignant neoplasm of female genital organ, unspecified
40671	Byu8.00	[X]Malignant neoplasm of male genital organs
57191	Byu8000	[X]Malignant neoplasm/other specified male genital organs
45262	Byu8200	[X]Malignant neoplasm of male genital organ, unspecified
35113	Byu9.00	[X]Malignant neoplasm of urinary tract
45260	Byu9000	[X]Malignant neoplasm of urinary organ, unspecified
35285	ByuA.00	[X]Malignant neoplasm of eye, brain and other parts of cent
68027	ByuA000	[X]Malignant neoplasm/other and unspecified cranial nerves
41515	ByuA100	[X]Malignant neoplasm/central nervous system, unspecified
63925	ByuA200	[X]Malignant neoplasm of meninges, unspecified
47633	ByuA300	[X]Malig neopl, overlap lesion brain & other part of CNS
40608	ByuB.00	[X]Malignant neoplasm of thyroid and other endocrine glands
64309	ByuB100	[X]Malignant neoplasm of endocrine gland, unspecified
35186	ByuC.00	[X]Malignant neoplasm of ill-defined, secondary and unspeci
39027	ByuC000	[X]Malignant neoplasm of other specified sites
96226	ByuC100	[X]Malignant neoplasm/overlap lesion/other+ill-defined sites
66163	ByuC200	[X]2ndry+unspcf malignant neoplasm lymph nodes/multi regions
57481	ByuC300	[X]Secondary malignant neoplasm/oth+unspc respiratory organs

88022	ByuC400	[X]Secondary malignant neoplasm/oth+unspcfd digestive organs
97091	ByuC500	[X]2ndry malignant neoplasm/bladder+oth+unsp urinary organs
68332	ByuC600	[X]2ndry malignant neoplasm/oth+unspec parts/nervous system
54253	ByuC700	[X]Secondary malignant neoplasm of other specified sites
52029	ByuC800	[X]Malignant neoplasm without specification of site
40740	ByuD.00	[X]Malignant neoplasms of lymphoid, haematopoietic and rela
43415	ByuD000	[X]Other Hodgkin's disease
67518	ByuD100	[X]Other types of follicular non-Hodgkin's lymphoma
98596	ByuD200	[X]Other types of diffuse non-Hodgkin's lymphoma
64336	ByuD300	[X]Other specified types of non-Hodgkin's lymphoma
102688	ByuD400	[X]Other malignant immunoproliferative diseases
67029	ByuD500	[X]Other lymphoid leukaemia
61693	ByuD600	[X]Other myeloid leukaemia
89762	ByuD700	[X]Other monocytic leukaemia
89329	ByuD800	[X]Other specified leukaemias
65165	ByuD900	[X]Other leukaemia of unspecified cell type
72500	ByuDB00	[X]Mal neoplasm/lymphoid,haematopoietic+related tissu,unspcf
64515	ByuDC00	[X]Diffuse non-Hodgkin's lymphoma, unspecified
63375	ByuDE00	[X]Unspecified B-cell non-Hodgkin's lymphoma
8649	ByuDF00	[X]Non-Hodgkin's lymphoma, unspecified type
7940	ByuDF11	[X]Non-Hodgkin's lymphoma NOS
63598	ByuE.00	[X]Malignant neoplasms/independent (primary) multiple sites
64897	ByuE000	[X]Malignant neoplasms/independent(primary)multiple sites

End-stage renal disease codes

medcode	readcode	readterm
2266	K04..00	Acute renal failure
2996	7L1A200	Haemodialysis NEC
6712	K050.00	End stage renal failure
2994	7L1A100	Peritoneal dialysis
11773	7L1A.11	Dialysis for renal failure
20196	14V2.00	H/O: renal dialysis
20073	7L1A000	Renal dialysis
8037	7L1B000	Insertion of ambulatory peritoneal dialysis catheter
25582	K04z.00	Acute renal failure NOS
8330	K0D..00	End-stage renal disease
24676	SK08.00	Acute renal failure due to rhabdomyolysis
22252	ZV45100	[V]Renal dialysis status
60302	7A60600	Creation of graft fistula for dialysis
23773	7L1B100	Removal of ambulatory peritoneal dialysis catheter
30709	7L1C000	Insertion of temporary peritoneal dialysis catheter
5475	7261011	Cyclodialysis
100205	K0E..00	Acute-on-chronic renal failure

64828	7L1A600	Peritoneal dialysis NEC
39993	F447C00	Iridodialysis
53852	K05..12	End stage renal failure
46438	SP05613	[X] Peritoneal dialysis associated peritonitis
30756	7L1A500	Continuous ambulatory peritoneal dialysis
59315	SP07G00	Stenosis of arteriovenous dialysis fistula
44422	14V2.11	H/O: kidney dialysis
48639	SP01500	Mechanical complication of dialysis catheter
36442	7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
52088	ZV56100	[V]Preparatory care for dialysis
88597	7L1A400	Automated peritoneal dialysis
52123	8882	Intestinal dialysis
69760	ZVu3G00	[X]Other dialysis
28158	TB11.00	Kidney dialysis with complication, without blame
46145	ZV56011	[V]Aftercare involving renal dialysis NOS
60446	Z919.00	Care of haemodialysis equipment
60743	ZV56.00	[V]Aftercare involving intermittent dialysis
96347	7A61900	Ligation of arteriovenous dialysis fistula
63502	Z91A.00	Peritoneal dialysis bag procedure
67494	7257300	Correction iridodialysis NEC
71651	F410400	New partial retinal detachment with retinal dialysis
72336	Z919100	Priming haemodialysis lines
105209	K045.00	Acute renal failure due to non-traumatic rhabdomyolysis
45160	ZV56y11	[V]Aftercare involving peritoneal dialysis
60498	Z919300	Reversing haemodialysis lines
66714	TB11.11	Renal dialysis with complication, without blame
101124	SP06B00	Continuous ambulatory peritoneal dialysis associated perit
63488	ZV56y00	[V]Other specified aftercare involving intermittent dialysis
101756	7L1A011	Thomas intravascular shunt for dialysis
101912	Z1A..00	Dialysis training
105739	K04..11	ARF - Acute renal failure
63038	ZV56z00	[V]Unspecified aftercare involving intermittent dialysis
69266	TA22000	Failure of sterile precautions during kidney dialysis
74905	Z1A2.00	Haemodialysis training
96184	TA02000	Accid cut,puncture,perf,h'ge - kidney dialysis
102210	7L1f000	Extracorporeal albumin haemodialysis
104719	Z1A1.00	Peritoneal dialysis training
99692	ZV56000	[V]Aftercare involving extracorporeal dialysis
104586	7L1B200	Flushing of peritoneal dialysis catheter
105436	SP0G.00	Anaphylactoid reaction due to haemodialysis
105742	G72D200	Aneurysm of anastomotic site of dialysis AV fistula
107188	G72D.00	Aneurysm of dialysis arteriovenous fistula
107220	G72D100	Aneurysm of needle site of dialysis arteriovenous fistula
107241	K043400	Acute renal failure induced by non-steroid anti-inflamm drug
86419	4N2..00	Dialysis fluid glucose level

98888	4I29.00	Peritoneal dialysis sample
101736	4N0..00	Dialysis fluid urea level
105760	G72C.00	Ruptured aneurysm of dialysis vascular access

Appendix 2 - Systematic review search strategy and forest plots

Medline Search strategy

1. HbA1c.mp.
2. Haemoglobin A1c.mp.
3. hemoglobin A1c.mp.
4. glycated haemoglobin.mp.
5. glycated hemoglobin.mp.
6. glycosylated hemoglobin.mp.
7. glycosylated haemoglobin.mp.
8. Hb A1c.mp.
9. A1c.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. ((immediate* or rapid* or same time or same visit or near patient or instant* or portable or bedside or bed-side or handheld or hand-held) adj3 (test* or turnaround or analys* or analyz* or measure* or assay* or monitor*)).tw.
12. (poc or poct or "point of care").tw.
13. Point-of-Care Systems/
14. A1cNow*.mp.
15. Afinion.mp.
16. NycoCard.mp.
17. DCA Vantage.mp.
18. in2it.mp.
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 10 and 19

Forest plots from meta-analysis

Fig A1 - Sensitivity analysis excluding studies in which estimates were made

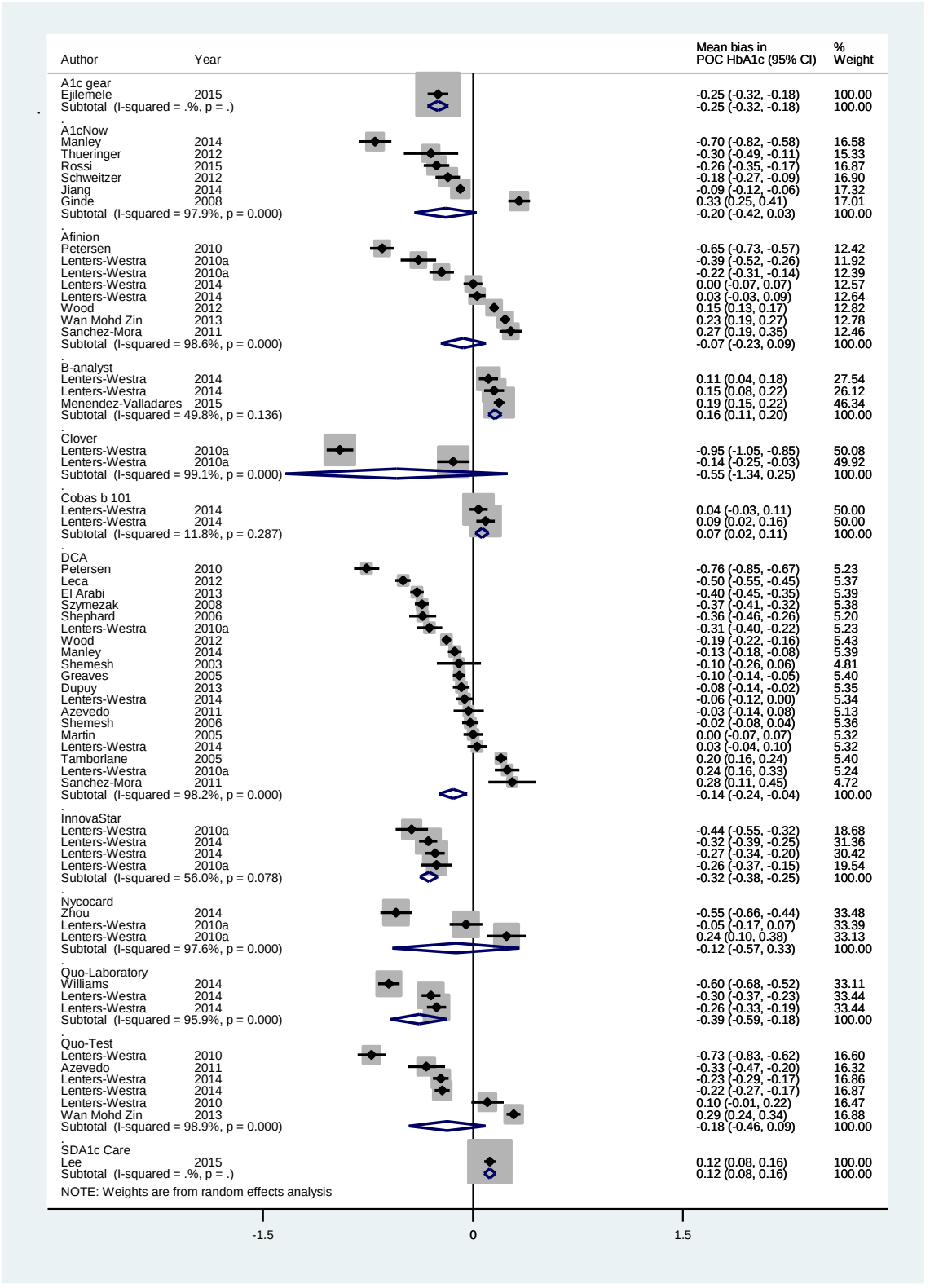


Fig A2 - Sensitivity analysis excluding studies which may be at risk of bias

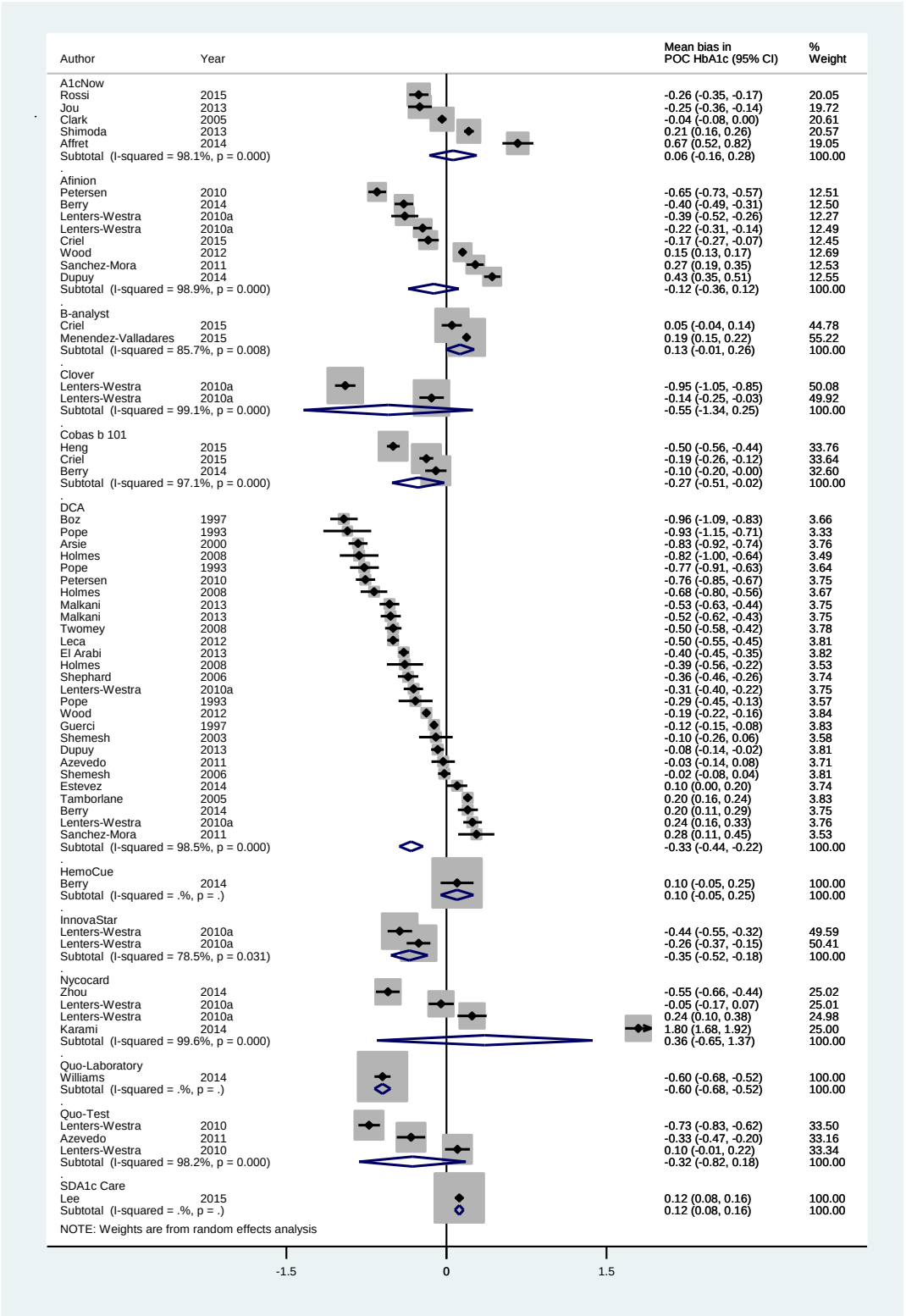


Figure A3 – Sensitivity analysis only including studies in NGSP-certified or accredited laboratories

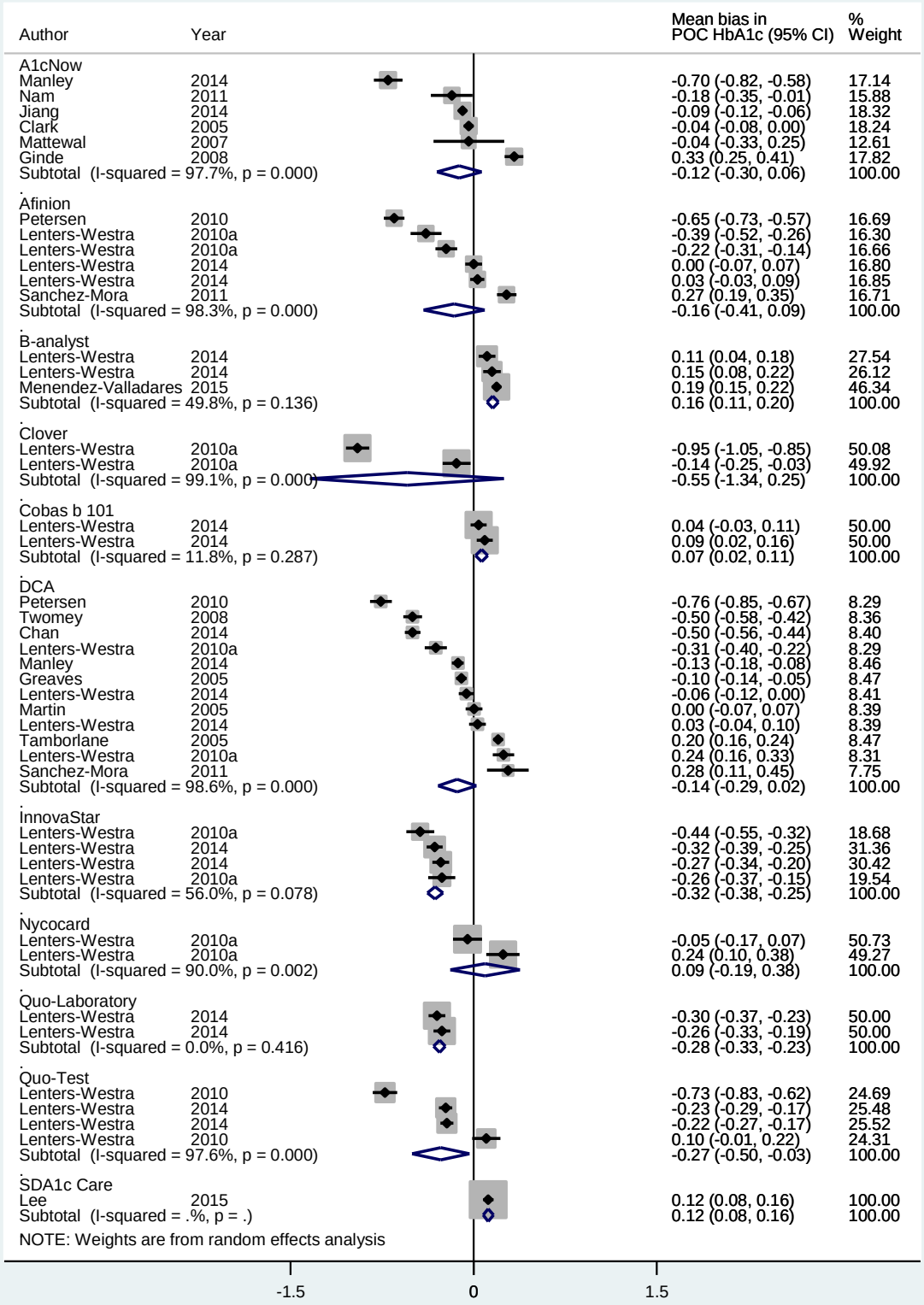


Figure A4 – Mean bias in studies using ion exchange laboratory method

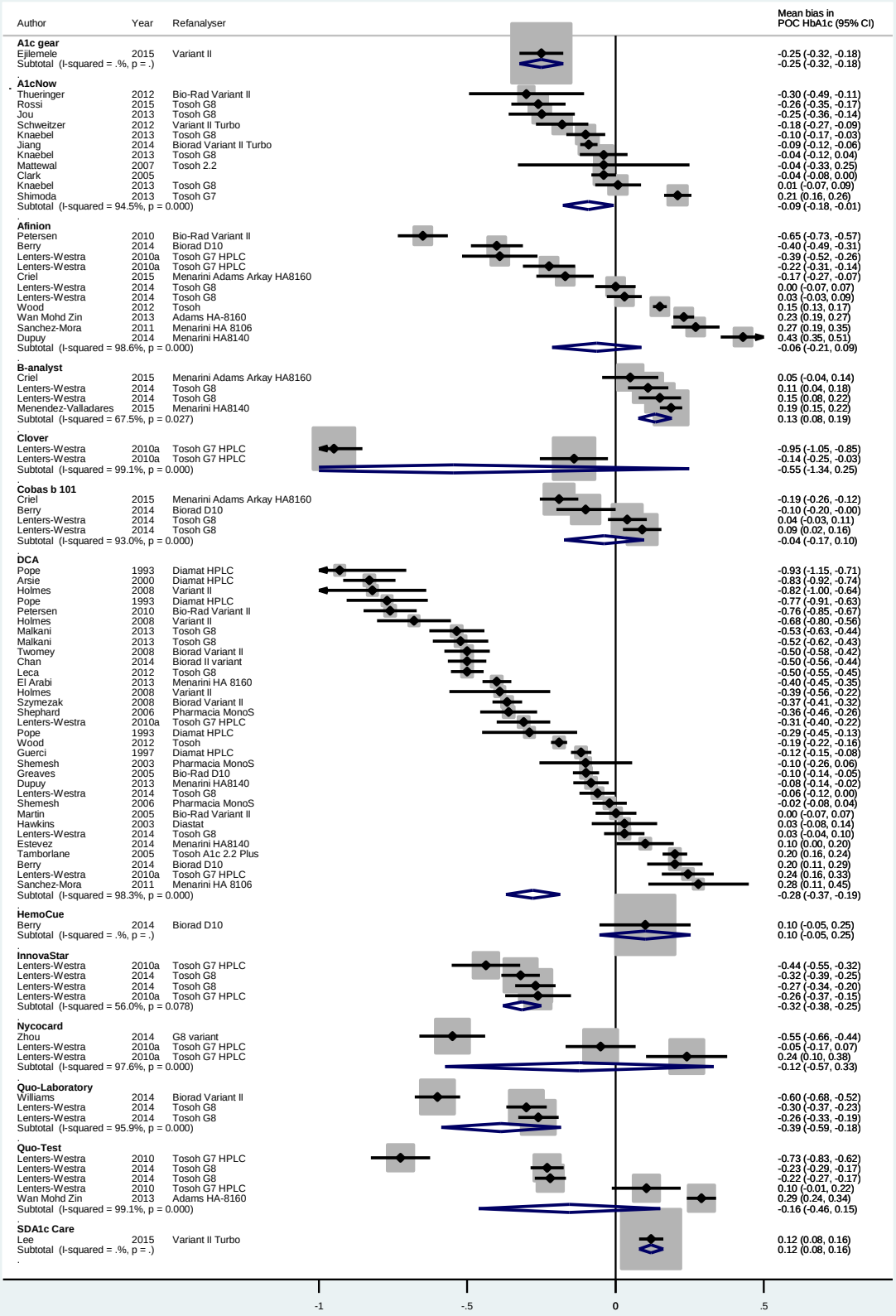


Figure A5 – Mean bias in studies published in 2014-2015

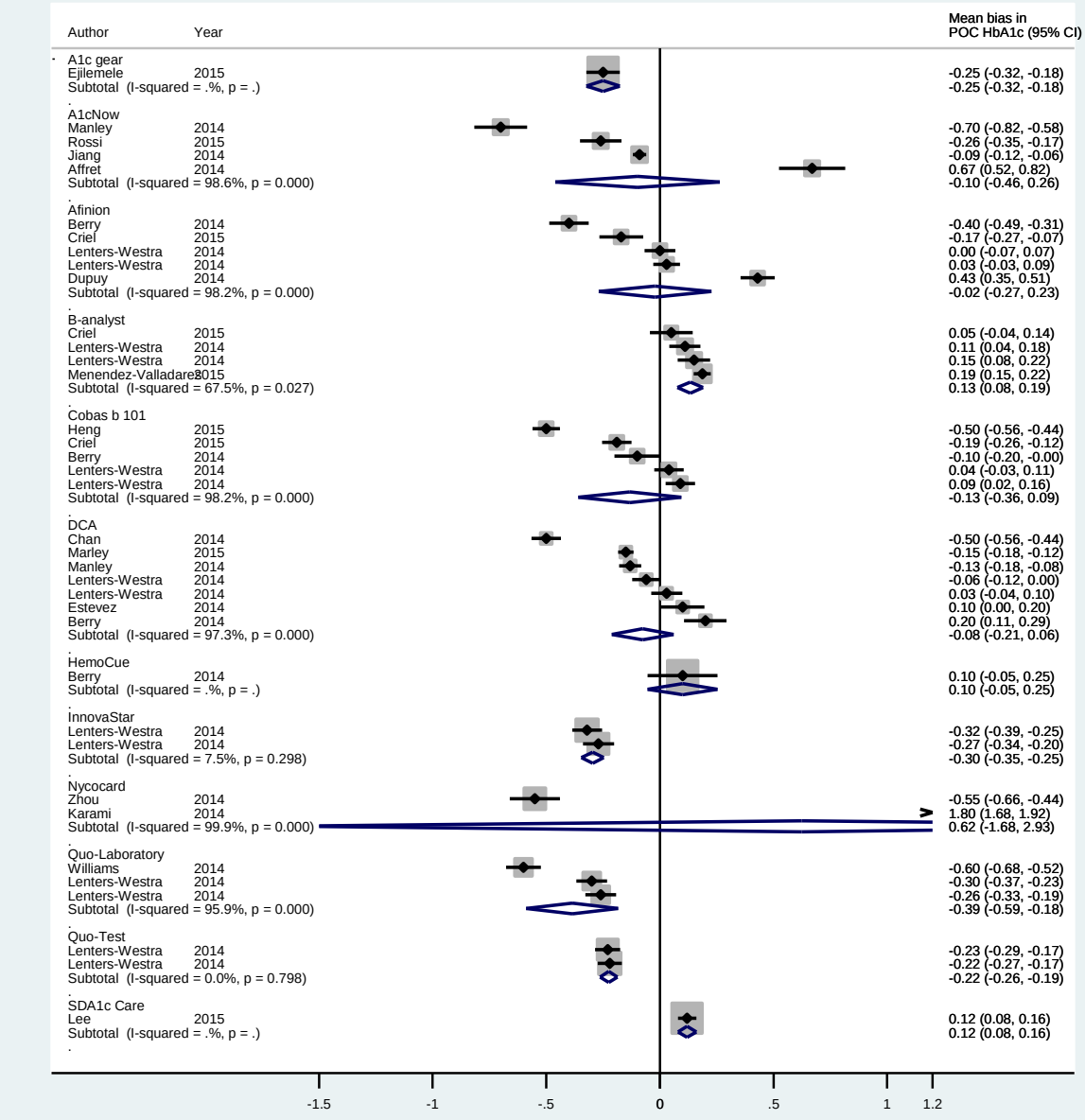


Figure A6 – Mean bias subgroup analysis of DCA device – POC vs lab setting

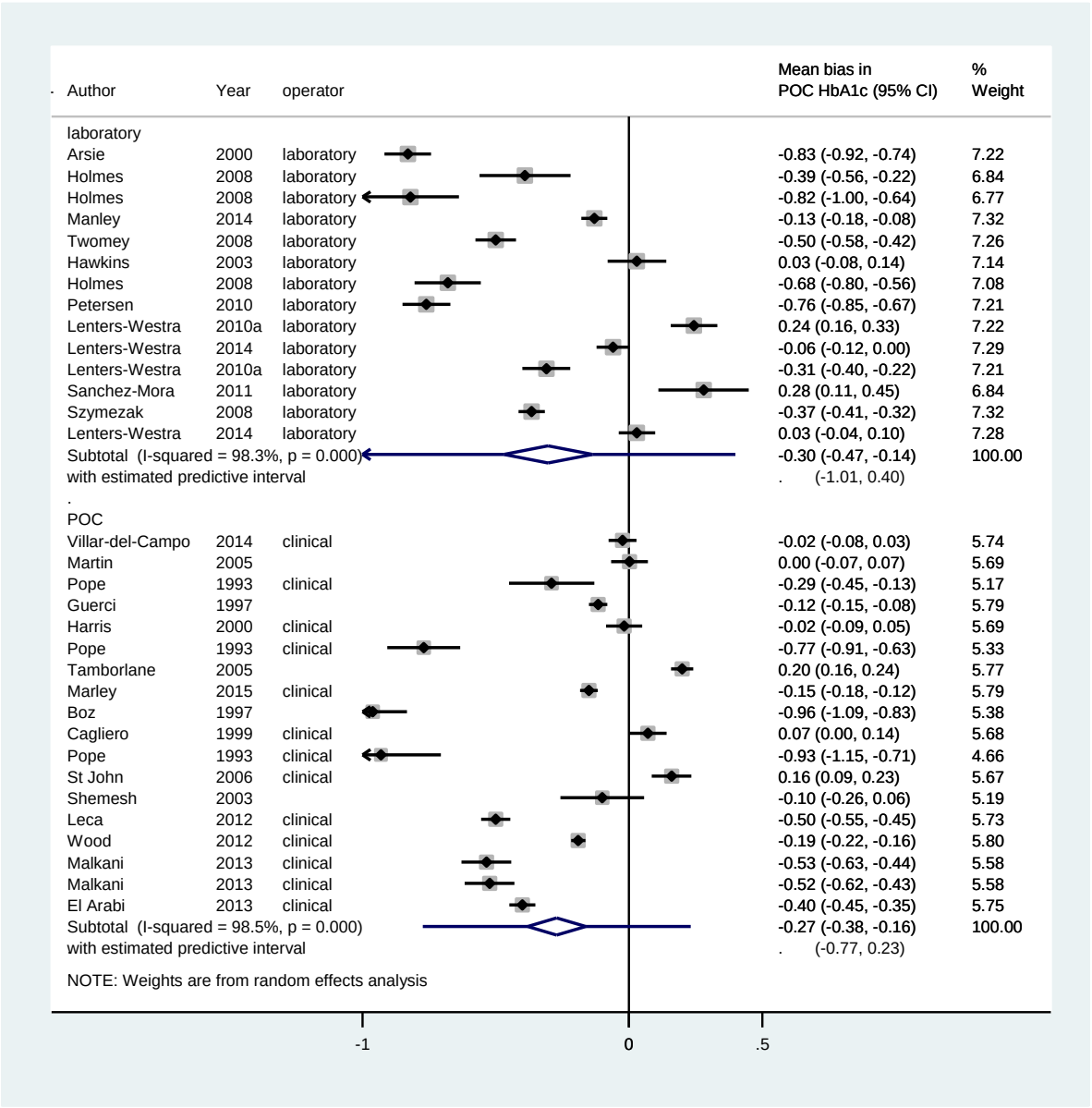


Figure A7 - Mean bias subgroup analysis of A1cNow device – POC vs lab setting

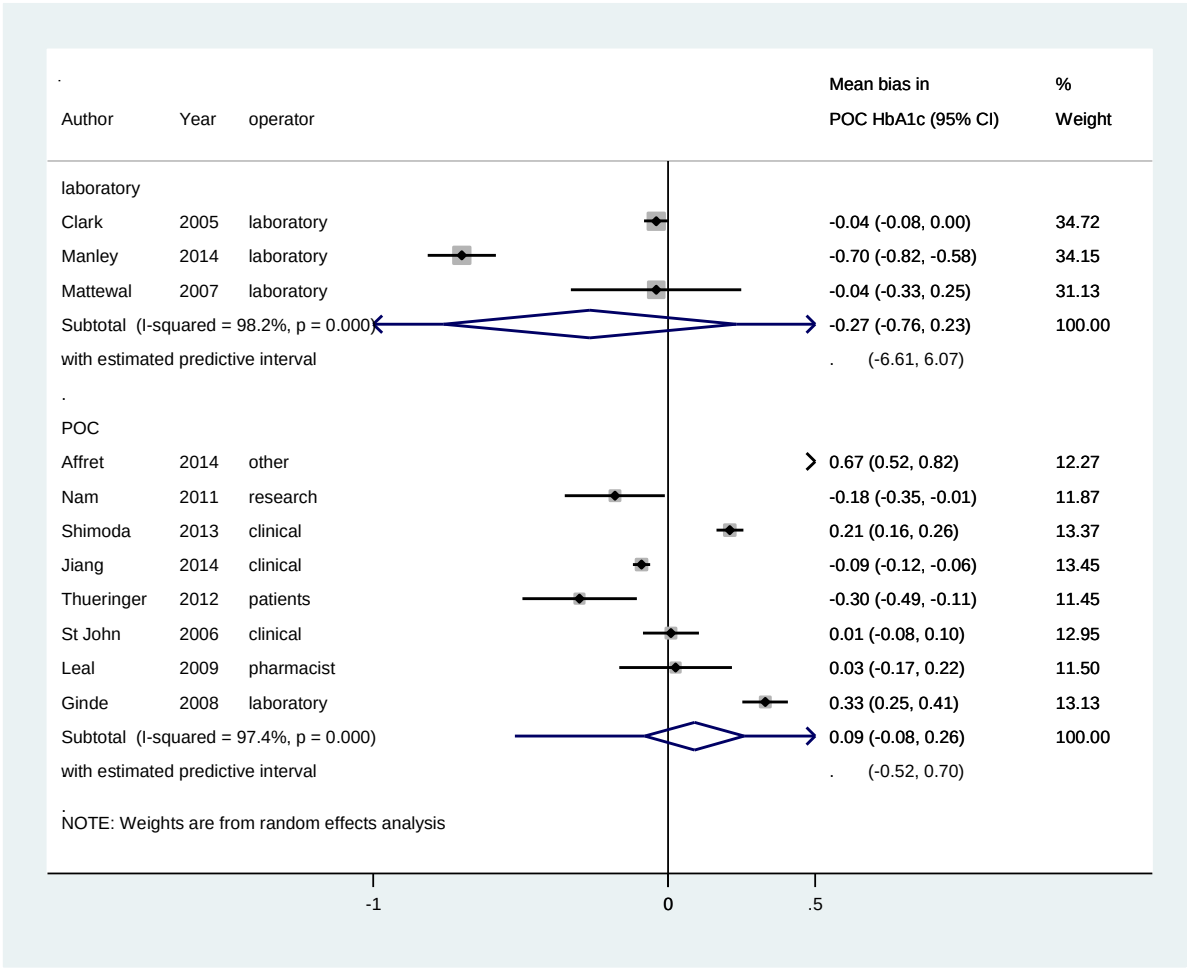


Figure A8 – Subgroup analysis of mean bias for DCA based on laboratory or clinical operator showing mean bias, 95% confidence intervals and prediction intervals. Studies are ordered by year of publication. (Some studies appear more than once as evaluations were carried out on multiple lot numbers)

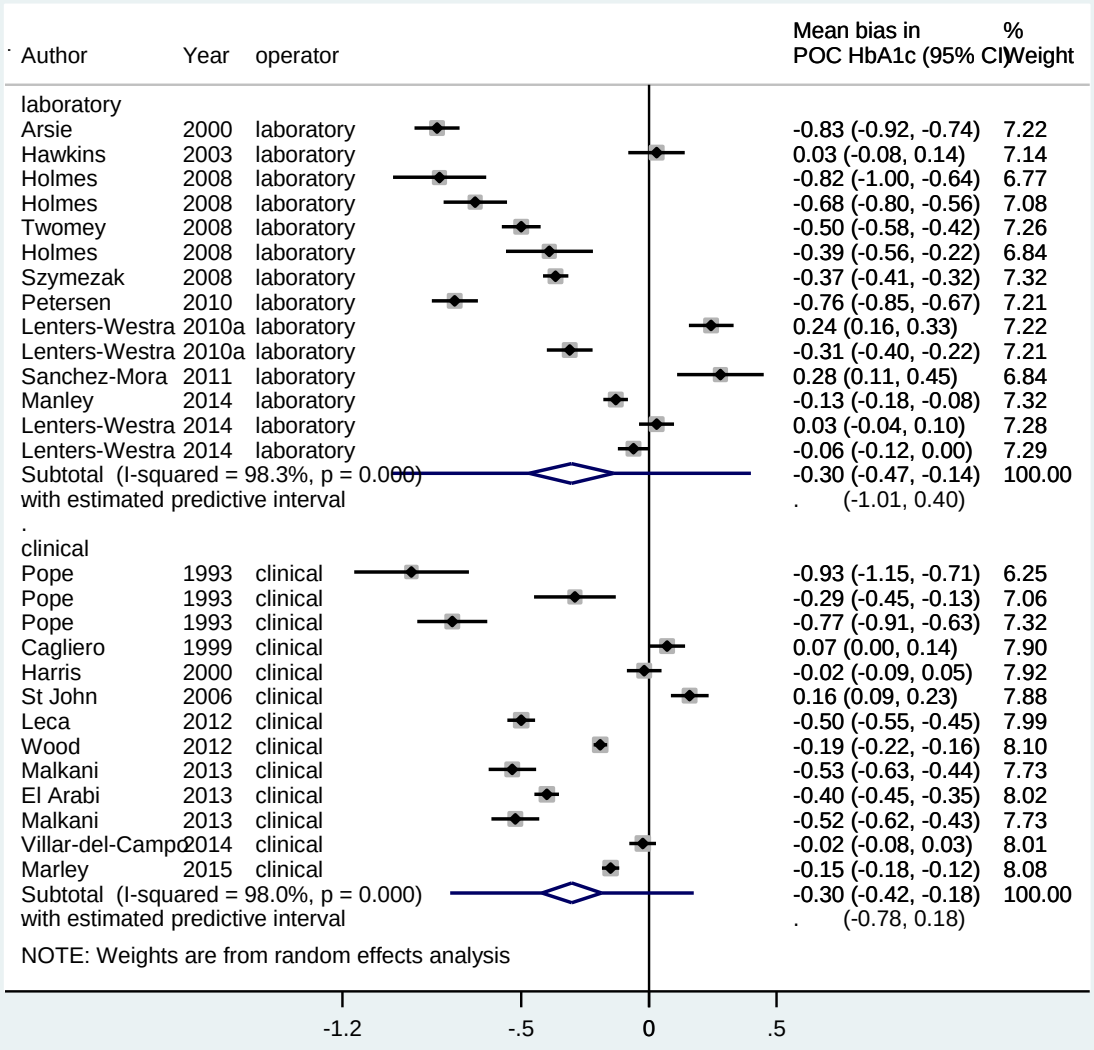


Figure A9 - Mean bias subgroup analysis of A1cNow device – 'Other' vs laboratory operator

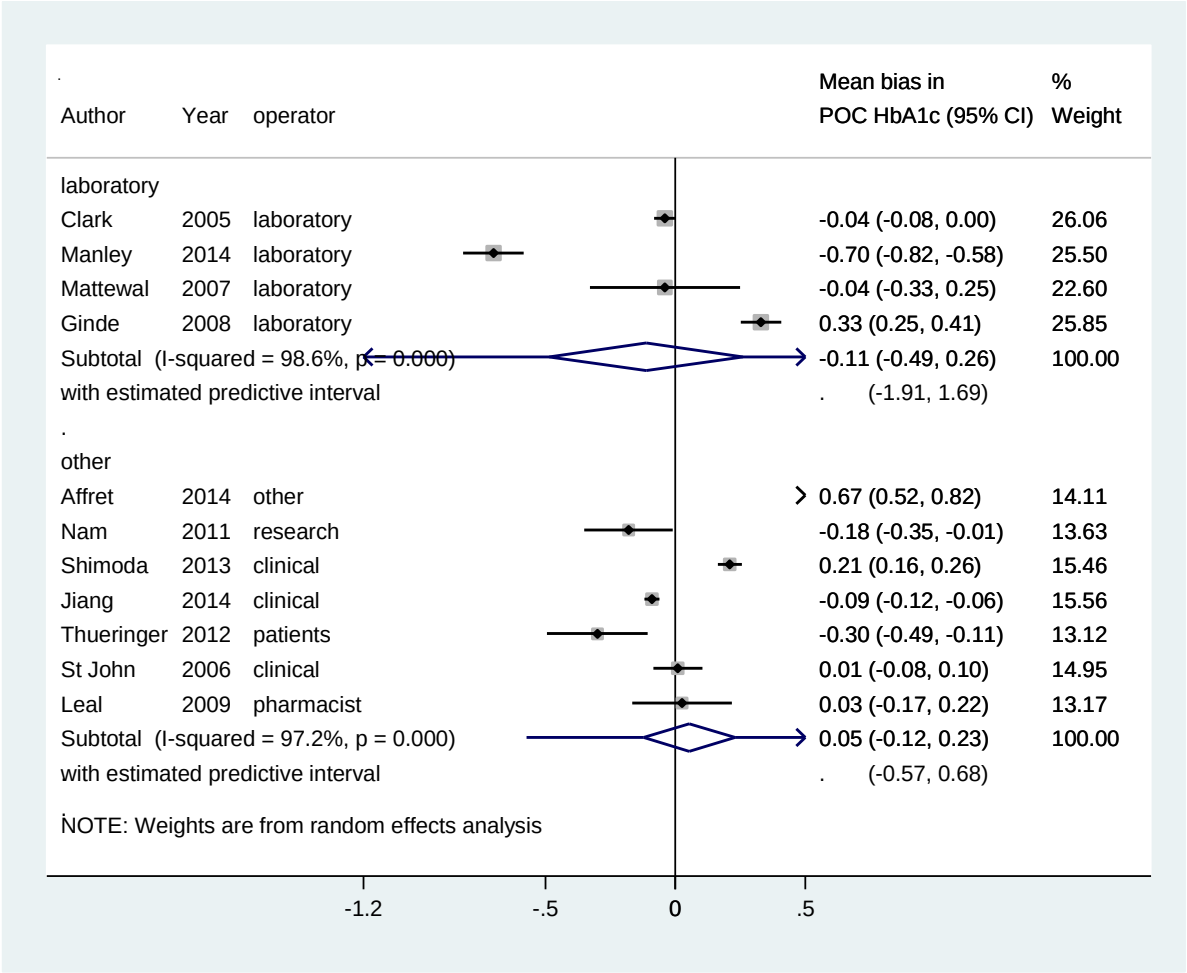


Figure A10 - Mean bias subgroup analysis of DCA device - Adults vs children

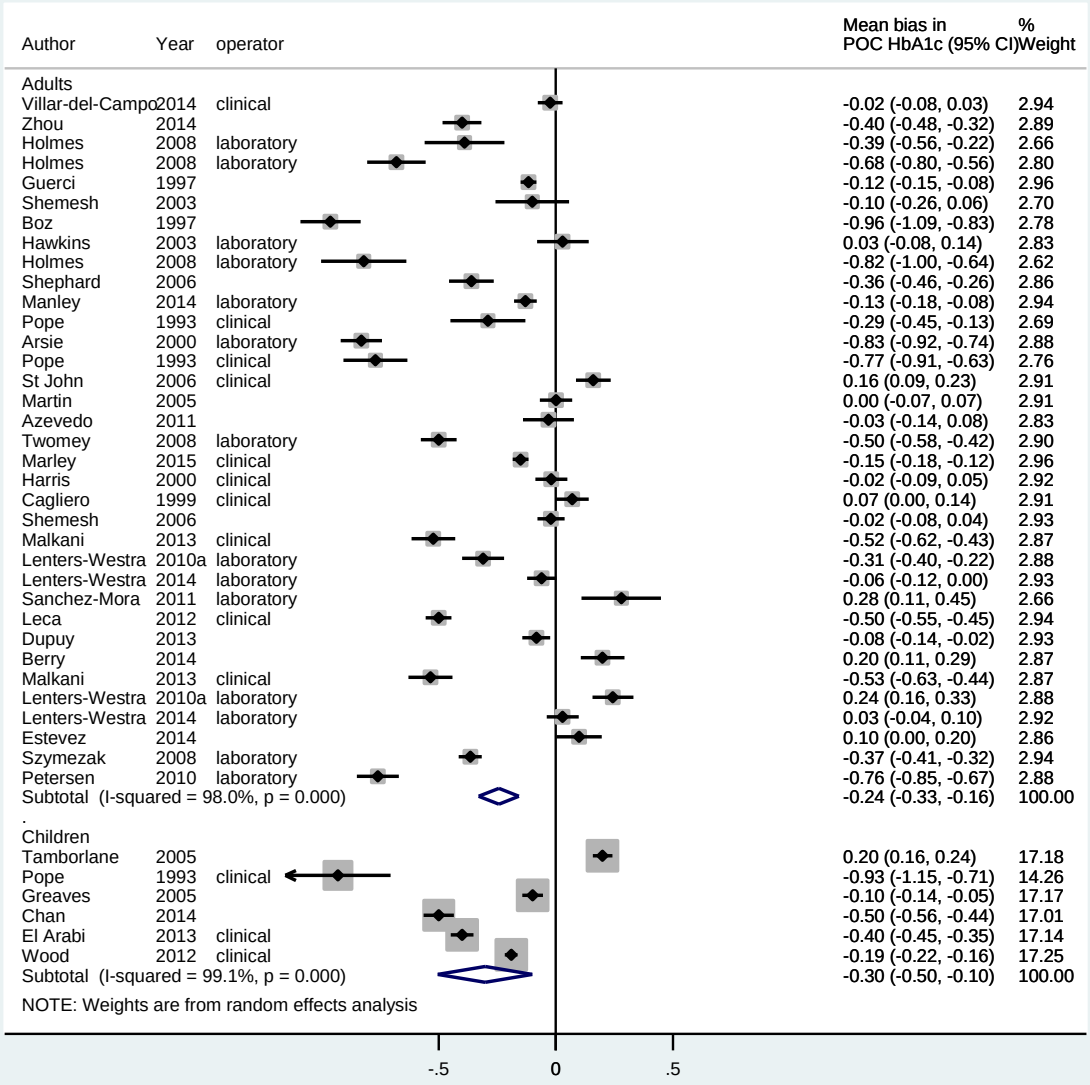


Figure A11 - Mean bias subgroup analysis of A1cNow device - venous vs capillary in A1cNow against venous reference

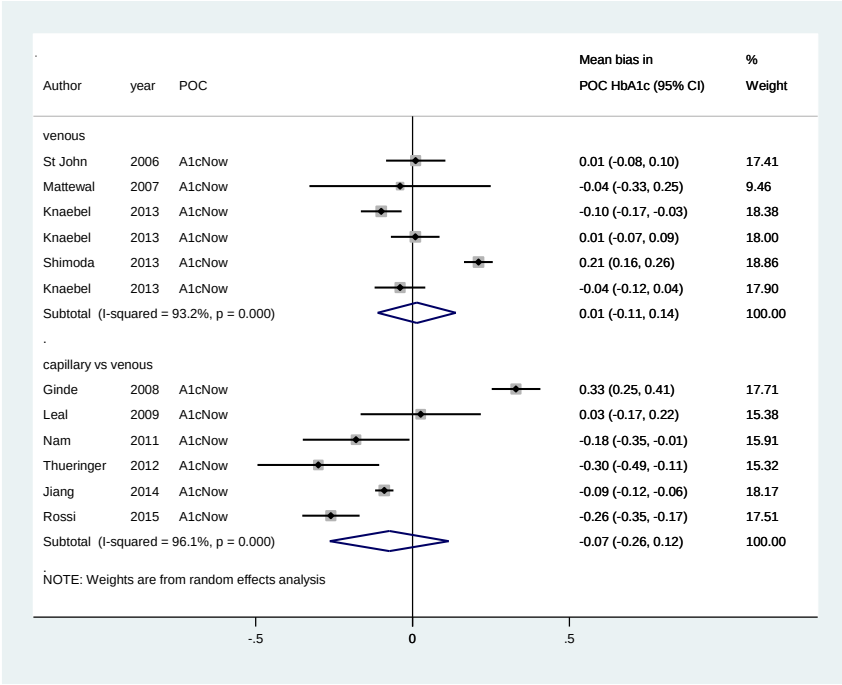
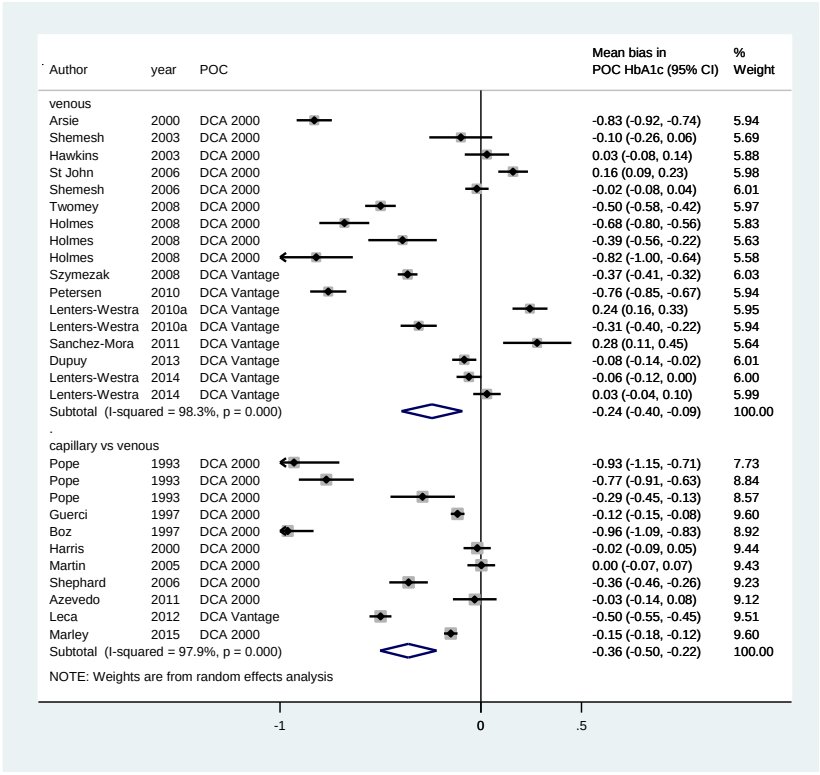


Figure A12 - Mean bias subgroup analysis of DCA device - venous vs capillary in DCA against venous reference



Appendix 3 - Study Questionnaires

DTSQ

Diabetes Treatment Satisfaction Questionnaire: DTSQs

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

most of the time	6	5	4	3	2	1	0	none of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

most of the time	6	5	4	3	2	1	0	none of the time

4. How convenient have you been finding your treatment to be recently?

very convenient	6	5	4	3	2	1	0	very inconvenient

5. How flexible have you been finding your treatment to be recently?

very flexible	6	5	4	3	2	1	0	very inflexible

6. How satisfied are you with your understanding of your diabetes?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Please make sure that you have circled one number on each of the scales.

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DTSQs © Prof Clare Bradley 9/93 Standard UK English (rev. 7/94)
Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK.

Appointment Satisfaction Questionnaire

Questions on HbA1c appointment

Please tick the most appropriate box or circle the answer which most corresponds how important this is to you; 6 if it is very important or 1 if it is not important at all.

1. Do you know why your HbA1c is being measured?

   ☐ Yes ☐ No ☐ Not sure

2. Do you think it is important to get an immediate result?

   Very important … Not important at all Don't know

   6 5 4 3 2 1 0

3. Do you think it is important to have time to discuss your HbA1c result with your doctor or nurse?

   Very important … Not important at all Don't know

   6 5 4 3 2 1 0

4. Knowing my HbA1c would help me to manage my diabetes

   ☐ True ☐ False ☐ Not sure

Please circle a number in the following questions to show your level of **satisfaction with your appointment today**:

5. The amount of time spent talking to the doctor or nurse

   Very satisfied … Very dissatisfied Don't know

   6 5 4 3 2 1 0

6. The advice given by the doctor or nurse

   Very satisfied … Very dissatisfied Don't know

   6 5 4 3 2 1 0

7. Continuity of care, that is whether you see the same doctor or nurse each visit

   Very satisfied … Very dissatisfied Don't know

   6 5 4 3 2 1 0

8. Discussing with the doctor or nurse any problems which I may have

Very satisfied					Very dissatisfied	Don't know
6	5	4	3	2	1	0

9. The extent to which I feel understood by the doctor or nurse

Very satisfied					Very dissatisfied	Don't know
6	5	4	3	2	1	0

10. Information given to me by the staff regarding my results

Very satisfied					Very dissatisfied	Don't know
6	5	4	3	2	1	0

11. How I am treated as a person by the staff?

Very satisfied					Very dissatisfied	Don't know
6	5	4	3	2	1	0

12. Time spent in the surgery during this appointment

Very satisfied					Very dissatisfied	Don't know
6	5	4	3	2	1	0

13. How satisfied are you overall with your appointment today?

Very satisfied					Very dissatisfied	Don't know
6	5	4	3	2	1	0

14. With what (if any) aspects of your appointment were you dissatisfied?

Please describe

15. How do you think your appointment could be improved?

Please describe

16. Do you feel that you understand the importance of maintaining good HbA1c control?

☐ Yes ☐ No ☐ Not sure

17. In your opinion is your diabetes well controlled now?

☐ Yes ☐ No ☐ Not sure

Revised Illness Perception Questionnaire

YOUR VIEWS ABOUT YOUR DIABETES

Listed below are a number of symptoms that you may or may not have experienced since your diabetes. Please indicate by circling *Yes* or *No*, whether you have experienced any of these symptoms since your diabetes, and whether you believe that these symptoms are related to your diabetes.

	I have experienced this symptom *since my diabetes*			This symptom is *related to my diabetes*	
Pain	**Yes**	**No**	_____	**Yes**	**No**
Sore Throat	**Yes**	**No**	_____	**Yes**	**No**
Nausea	**Yes**	**No**	_____	**Yes**	**No**
Breathlessness	**Yes**	**No**	_____	**Yes**	**No**
Weight Loss	**Yes**	**No**	_____	**Yes**	**No**
Fatigue	**Yes**	**No**	_____	**Yes**	**No**
Stiff Joints	**Yes**	**No**	_____	**Yes**	**No**
Sore Eyes	**Yes**	**No**	_____	**Yes**	**No**
Wheeziness	**Yes**	**No**	_____	**Yes**	**No**
Headaches	**Yes**	**No**	_____	**Yes**	**No**
Upset Stomach	**Yes**	**No**	_____	**Yes**	**No**
Sleep Difficulties	**Yes**	**No**	_____	**Yes**	**No**
Dizziness	**Yes**	**No**	_____	**Yes**	**No**
Loss of Strength	**Yes**	**No**	_____	**Yes**	**No**

We are interested in your own personal views of how you now see your current diabetes.

Please indicate how much you agree or disagree with the following statements about your diabetes by ticking the appropriate box.

	VIEWS ABOUT YOUR DIABETES	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
IP1	My diabetes will last a short time					
IP2	My diabetes is likely to be permanent rather than temporary					
IP3	My diabetes will last for a long time					

	VIEWS ABOUT YOUR DIABETES	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
IP4*	This diabetes will pass quickly					
IP5*	I expect to have this diabetes for the rest of my life					
IP6	My diabetes is a serious condition					
IP7	My diabetes has major consequences on my life					
IP8*	My diabetes does not have much effect on my life					
IP9	My diabetes strongly affects the way others see me					
IP10	My diabetes has serious financial consequences					
IP11	My diabetes causes difficulties for those who are close to me					
IP12	There is a lot which I can do to control my symptoms					
IP13	What I do can determine whether my diabetes gets better or worse					
IP14	The course of my diabetes depends on me					
IP15*	Nothing I do will affect my diabetes					
IP16	I have the power to influence my diabetes					
IP17*	My actions will have no affect on the outcome of my diabetes					
IP18*	My diabetes will improve in time					
IP19*	There is very little that can be done to improve my diabetes					
IP20	My treatment will be effective in curing my diabetes					
IP21	The negative effects of my diabetes can be prevented (avoided) by my treatment					
IP22	My treatment can control my diabetes					
IP23*	There is nothing which can help my condition					
IP24	The symptoms of my condition are puzzling to me					
IP25	My diabetes is a mystery to me					

IP26	I don=t understand my diabetes					
IP27	My diabetes doesn=t make any sense to me					
IP28*	I have a clear picture or understanding of my condition					
IP29	The symptoms of my diabetes change a great deal from day to day					
IP30	My symptoms come and go in cycles					
IP31	My diabetes is very unpredictable					
IP32	I go through cycles in which my diabetes gets better and worse.					
IP33	I get depressed when I think about my diabetes					
IP34	When I think about my diabetes I get upset					
IP35	My diabetes makes me feel angry					
IP36*	My diabetes does not worry me					
IP37	Having this diabetes makes me feel anxious					
IP38	My diabetes makes me feel afraid					

CAUSES OF MY DIABETES

We are interested in what you consider may have been the cause of your diabetes. As people are very different, there is no correct answer for this question. We are most interested in your own views about the factors that caused your diabetes rather than what others including doctors or family may have suggested to you. Below is a list of possible causes for your diabetes. Please indicate how much you agree or disagree that they were causes for you by ticking the appropriate box.

	POSSIBLE CAUSES	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
C1	Stress or worry					
C2	Hereditary - it runs in my family					
C3	A Germ or virus					
C4	Diet or eating habits					
C5	Chance or bad luck					
C6	Poor medical care in my past					
C7	Pollution in the environment					
C8	My own behaviour					
C9	My mental attitude e.g. thinking about life negatively					
C10	Family problems or worries					
C11*	Overwork					
C12*	My emotional state e.g. feeling down, lonely, anxious, empty					
C13*	Ageing					
C14*	Alcohol					
C15*	Smoking					
C16*	Accident or injury					
C17*	My personality					
C18*	Altered immunity					

In the table below, please list in rank-order the three most important factors that you now believe caused YOUR diabetes. You may use any of the items from the box above, or you may have additional ideas of your own.

The most important causes for me:

1. _____
2. _____
3. _____

Patient Activation Measure - PAM



Below are some statements that people sometimes make when they talk about their health. Please indicate how much you agree or disagree with each statement as it applies to you personally by circling your answer. Your answers should be what is true for you and not just what you think the doctor wants you to say.

If the statement does not apply to you, circle N/A.

1. When all is said and done, I am the person who is responsible for taking care of my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
2. Taking an active role in my own health care is the most important thing that affects my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
3. I know what each of my prescribed medications do	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
4. I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
5. I am confident that I can tell a doctor concerns I have even when he or she does not ask.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
6. I am confident that I can follow through on medical treatments I may need to do at home	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
7. I have been able to maintain (keep up with) lifestyle changes, like eating right or exercising	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
8. I know how to prevent problems with my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
9. I am confident I can figure out solutions when new problems arise with my health.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
10. I am confident that I can maintain lifestyle changes, like eating right and exercising, even during times of stress.	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A

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MMAS

Point-of-care HbA1c Testing
(REC No: 14/NI/1127)

POC HbA1c

Morisky Medical Adherence Questionnaire

Participant ID number | | / | | | / | | |

Date (*Eg.* 01Jan2015) D D M M M Y Y Y Y

People with diabetes sometimes forget to take their pills or miss them. We are interested in how often you have taken yours

Do you sometimes forget to take your diabetes medicine? ☐ yes ☐ no

Over the past two weeks, were there any days when you did not take your diabetes medicine? ☐ yes ☐ no

Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it? ☐ yes ☐ no

When you travel or leave home, do you sometimes forget to bring along your medications? ☐ yes ☐ no

Did you take your diabetes medicine yesterday? ☐ yes ☐ no

When you feel like your diabetes is under control, do you sometimes stop taking your diabetes medicine? ☐ yes ☐ no

Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your diabetes treatment plan? ☐ yes ☐ no

How often do you have difficulty remembering to take all your diabetes medication? *(please circle one)*

Never/rarely	0
Once in a while	1
Sometimes	2
Usually	3
All the time	4

Appendix 4 - Qualitative interview schedule

Appendix 4 - Interview schedule

Hello, my name is Jenny Hirst

Thank you very much for agreeing to take part in these interviews. I'm a researcher form University of Oxford who is working on this study. I'd just like to go through a few things with you before we start. You have already had one visit with your GP or nurse, are there any questions which you would like to ask me about the study?

I would like to check that it's OK with you that I audio record the interview so I don't need to take notes while I am speaking to you. The recording will be typed up, and your name will not be used in the typed copy so it will be completely anonymous. Are you happy for me to record this interview?

I would also like to assure you that only the research team will have access to what you say today, it will not be made available to anyone in the GP surgery.

Could we now go through the consent form?
Each item will be read out and the participant will be asked to sign.

Is there anything else you would like to ask before we begin?

As you are aware you are taking part in a study to see whether point-of-care HbA1c testing can improve care in the GP surgery for people with diabetes. So far you have already had one study visit and given a blood sample to have your HbA1c measured in the hospital lab. You will be having 2 more study visits where you will have your HbA1c tested using the point-of-care test. Today I would like to hear about your diabetes and what you think about point-of-care testing.

There are no right or wrong answers to any of the questions I am going to ask you and negative feedback is just as useful as positive feedback.

Patient interview questions:

Questions specific to pre-POC interview:

1. Could you tell me about your diabetes and how it affects your health on a daily basis?
2. Please explain what you understand about HbA1c.
3. Do any of your family or friends also have diabetes?
4. How often do you usually see your GP about your diabetes
5. Could you describe what happens during your diabetes appointments
6. Typically how often do you get your HbA1c tested and how do you get your result?
7. Is there usually a chance to discuss the result with your doctor or nurse?
8. Do you know what your HbA1c *should* be?
9. How is your HBA1c target decided and how you go about achieving this?
10. How easy do you find it to talk with your GP/nurse about your diabetes and your treatment?
11. Are you happy with the treatment you receive from you GP?
12. Do you feel you have a good understand your diabetes?
13. How confident do you feel about managing your diabetes yourself?
14. What do you understand about HbA1c point-of-care testing?
15. How do you feel about your GP/nurse using POC testing for measuring your HbA1c?
16. How do you think this type of testing could change your diabetes care?
17. Can you think of any difficulties this type of testing may bring?
18. Do you expect POC testing to be more of less convenient to you?
19. Have you got any other comments or concerns?

Questions specific to post-POC interview

1. Overall how do you feel about having your HbA1c measured using POC testing over the past 3 months?
2. How has it affected your understanding of your diabetes?
3. How has it affected the way you manage your diabetes?
4. Were there any changes in the way you communicated with your doctor/nurse?
5. Who made the decision about your HBA1c target and what you should do to achieve it?
6. How many surgery staff did you see at each visit and who did what?
7. What did you think about the appointment times?
8. Did you find the POC testing more or less painful than your usual HbA1c test?
9. What benefits do you think this type of testing could bring to you?
10. Can you think of any difficulties which POC testing may bring?
11. Overall was the POC test more or less convenient for you than your usual test?
12. Is there anything you would like to see changed?
13. How could your experience be improved?
14. Have you got any other comments or concerns?

Clinician interview questions:

Clinician interview – post POC testing

1. What are your overall feelings about POC HbA1c testing?
2. How was using the device integrated into the patient appointments?
3. How many surgery staff were involved in each patient appointment?
4. Typically what was the care path for a patient?
5. How do you think using the device impacted on patient treatment times?
6. Was there always an opportunity to discuss the result with the patient?
7. How do you think this type of testing impacted on the patient consultation?
8. How do you think this type of testing had an impact on patient care?
9. Was the POC testing more or less convenient than the usual HbA1c test?
10. What are your feelings about the device accuracy?
11. What are your views on the costs to the surgery of using these devices?
12. What do you feel are the main benefits to this type of testing?
13. What do you feel are the main difficulties in using this type of testing?
14. Is there anything you would like to see changed?
15. Is there anything you can think of that would improve your experience?
16. Have you got any other comments or concerns?